ORIGINAL ARTICLE

Obecabtagene Autoleucel in Adults with B-Cell Acute Lymphoblastic Leukemia

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ABSTRACT

Obecabtagene autoleucel (obe-cel) is an autologous 41BB-ζ anti-CD19 chimeric antigen receptor (CAR) T-cell therapy which uses an intermediate-affinity CAR to reduce toxic effects and improve persistence.

METHODS

We conducted a phase 1b–2 multicenter study of obe-cel in adults (≥18 years of age) with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). The main cohort, cohort 2A, included patients with morphologic disease; patients in cohort 2B had measurable residual disease. The primary end point was overall remission (complete remission or complete remission with incomplete hematologic recovery) in cohort 2A. Secondary end points included event-free survival, overall survival, and safety.

RESULTS

Of the 153 enrolled patients, 127 (83.0%) received at least one infusion of obe-cel and were evaluable. In cohort 2A (94 patients; median follow-up, 20.3 months), overall remission occurred in 77% (95% confidence interval [CI], 67 to 85), with complete remission in 55% (95% CI, 45 to 66) and complete remission with incomplete hematologic recovery in 21% (95% CI, 14 to 31). The prespecified null hypotheses of overall remission (≤40%) and complete remission (≤20%) were rejected (P<0.001). In the 127 patients who received at least one obe-cel infusion (median follow-up, 21.5 months), the median event-free survival was 11.9 months (95% CI, 8.0 to 22.1); estimated 6- and 12-month event-free survival was 65.4% and 49.5%, respectively. The median overall survival was 15.6 months (95% CI, 12.9 to not evaluable); estimated 6- and 12-month overall survival was 80.3% and 61.1%, respectively. Grade 3 or higher cytokine release syndrome developed in 2.4% of the patients, and grade 3 or higher immune effector cell–associated neurotoxicity syndrome developed in 7.1% of the patients.

CONCLUSIONS

Obe-cel resulted in a high incidence of durable response among adults with relapsed or refractory B-cell ALL, with a low incidence of grade 3 or higher immune-related toxic effects. (Funded by Autolus Therapeutics; FELIX ClinicalTrials.gov number, NCT04404660.)

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Chimeric antigen receptor (CAR) T-cell therapy can induce sustained responses in relapsed or refractory B-cell cancers, including B-cell acute lymphoblastic leukemia (ALL).[1] Tisagenlecleucel (tisa-cel) has been available for children and young adults (≤25 years of age) with relapsed or refractory B-cell ALL since 2017 in the United States and 2018 in Europe.[1-3] Brexucabtagene autoleucel (brexu-cel) has recently been licensed for adults 18 years of age or older with relapsed or refractory B-cell ALL.[4-6]

Obecabtagene autoleucel (obe-cel) is an autologous 41BB-ζ anti-CD19 CAR T-cell therapeutic. Unlike tisa-cel and brexu-cel, which both use the same high-affinity single-chain variable fragment (scFv) to recognize CD19, obe-cel uses a different scFv with intermediate affinity due to a fast binding off-rate, which is hypothesized to reduce toxic effects and improve CAR T-cell engraftment and persistence.[7] Phase 1 testing of obe-cel in children and young adults with relapsed or refractory B-cell ALL[7] resulted in a high incidence of response, durable persistence, and a low incidence of severe immune-related toxic effects.

Obe-cel was subsequently tested in the phase 1 ALLCAR19 study involving adults 18 years of age or older with relapsed or refractory B-cell ALL.[8] Given the increased susceptibility of adults with B-cell ALL to immune-related toxic effects,[9] a bone marrow burden–guided split-dose regimen was used. Obe-cel showed high efficacy, with an incidence of measurable residual disease (MRD)–negative remission of 85% and a low incidence of grade 3 or higher cytokine release syndrome (0%) and immune effector cell–associated neurotoxicity syndrome (ICANS; 15%); a total of 36% of the patients were in ongoing remission at a median follow-up of 43 months.[10] Here, we report findings from the FELIX study, a multinational phase 1b–2 pivotal registration study, designed to continue the exploration of the safety, efficacy, and scalability of obe-cel in adults with relapsed or refractory B-cell ALL.

METHODS

STUDY DESIGN AND CONDUCT

The FELIX study was conducted at 34 sites in Spain, the United Kingdom, and the United States. The investigators are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. Eligible patients were 18 years of age or older and had relapsed or refractory CD19-positive B-cell ALL. Eligibility is detailed in the Supplementary Appendix; inclusion and exclusion criteria are listed in Tables S1 and S2 in the Supplementary Appendix. Black patients were underrepresented (Table S3).

The FELIX study had phase 1b and phase 2 components. Phase 1b involved two cohorts: cohort 1A, for patients with morphologic disease (≥5% bone marrow blasts), and cohort 1B, for those with MRD (<5% bone marrow blasts). The phase 2 component involved a main pivotal cohort — cohort 2A, for patients with morphologic disease at enrollment — as well as two exploratory cohorts: cohort 2B, for patients with MRD, and cohort 2C, for those with isolated extramedullary disease.

All the patients provided written informed consent. After the institutional review board approved the study protocol, the study was conducted in accordance with the principles of the Declaration of Helsinki. The study sponsor, Autolus Therapeutics, provided the authors with access to all study information necessary to prepare the manuscript; the raw data were available to all the authors for their review and analysis. The authors were required to protect confidential data and information provided by the sponsor and to respect any existing or future data embargoes.

The author contributions are detailed in Table S4. The first draft of the manuscript was written by the first and last authors, with medical writing assistance funded by the sponsor. All the authors contributed to the manuscript writing. The authors vouch for the completeness and accuracy of the data and for the adherence of the study to the protocol (available at NEJM.org).

Eligible patients underwent leukapheresis to allow manufacture of obe-cel (Fig. S1). Bridging therapy, except with blinatumomab, was permitted at the investigator's discretion. Obe-cel was administered in a bone marrow burden–adjusted split dose after lymphodepletion, with bone marrow assessment mandated before lymphodepletion to guide the dose. The second obe-cel dose was given in the absence of severe or unresolved toxic effects (Fig. S2). Disease assessment, lymphodepletion, dose administered, management of toxic effects, and study design are detailed in the Supplementary Appendix.

ASSESSMENTS AND STUDY END POINTS

The enrolled population comprised all the patients who were enrolled in the study, with enrollment defined as when the patient met all the inclusion criteria and none of the exclusion criteria and when patient leukapheresate (an apheresis product enriched for peripheral-blood mononuclear cells, including a high concentration of T cells) was sufficient for the manufacture of obe-cel. The infused population comprised all the patients who received at least one obe-cel infusion. The safety population was the same as the infused population.

The primary end point was overall remission (complete remission or complete remission with incomplete hematologic recovery) in cohort 2A, and the key secondary end point was complete remission in this cohort. Response evaluations were performed by an independent response review committee, which used the morphologic response criteria for ALL according to the adapted NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology, version 2.2019[11] (full citation provided in the Supplementary Appendix).

Other secondary end points included remission duration, event-free survival, MRD-negative remission, overall survival, progression-free survival, relapse-free survival, safety, stem-cell transplantation, and overall remission without stem-cell transplantation or other subsequent therapies. Study objectives and end points, end-point definitions, and response criteria are provided in Tables S5, S6, and S7, respectively.

STATISTICAL ANALYSIS

The primary end point of overall remission (complete remission or complete remission with incomplete hematologic recovery) in cohort 2A was first tested against the null hypothesis of 40% or less for the infused population. If that was achieved, the key secondary end point of complete remission in cohort 2A was tested against the null hypothesis of 20% or less. The thresholds of 40% for overall remission and 20% for complete remission were based on phase 3 trial experience with blinatumomab. Patients who were recruited to the FELIX study could be either exposed or not exposed to blinatumomab. The set thresholds were between the incidence of overall remission and the incidence of complete remission that would be expected with either blinatumomab or salvage chemotherapy (see sections 2.3.1 and 2.3.2 in the statistical analysis plan, available with the protocol).

These two end points were first tested in the prespecified efficacy interim analysis when 50 patients from cohort 2A had received an infusion of obe-cel and had been followed for 3 months or had been withdrawn from the study before the month 3 visit. The analysis was performed by means of an alpha-spending approach according to Lan–DeMets (O'Brien–Fleming). If either the primary or key secondary end point was not rejected at the efficacy interim analysis, the end points were to be tested again at the primary analysis according to the prespecified alpha-spending approach, so that the family-wise type I error at the one-sided 2.5% level was controlled throughout the testing sequence. All other prespecified end points and analyses for other cohorts were summarized descriptively.

Time-to-event end points were analyzed with the use of the Kaplan–Meier method. Data from patients who received new nonprotocol anticancer therapies, including stem-cell transplantation, were censored for the analysis of response duration and event-free survival. Additional statistical analysis methods are detailed in the Supplementary Appendix.

RESULTS

ENROLLMENT, MANUFACTURE, AND INFUSION

In total, 153 patients with relapsed or refractory B-cell ALL were enrolled in the combined phase 1b–2 FELIX study (Fig. 1). Obe-cel was successfully released for 146 of 153 patients (95.4%) at a median of 21 days (range, 18 to 50) after leukapheresis (Fig. S1B). Of the 153 enrolled patients, 127 (83.0%) received at least one obe-cel infusion and were evaluable; 26 of 153 did not receive an infusion, owing to physician choice in 1 patient, manufacturing failure in 7, and death or uncontrolled disease in 18 (Table S8). Four patients did not receive the full target dose owing to low manufacture yield. Feasibility of manufacturing is detailed in the Supplementary Results section of the Supplementary Appendix, and product characteristics are detailed in Figure S3.

PATIENT CHARACTERISTICS

Patient characteristics in cohort 2A and the total infused population are summarized in Table 1.

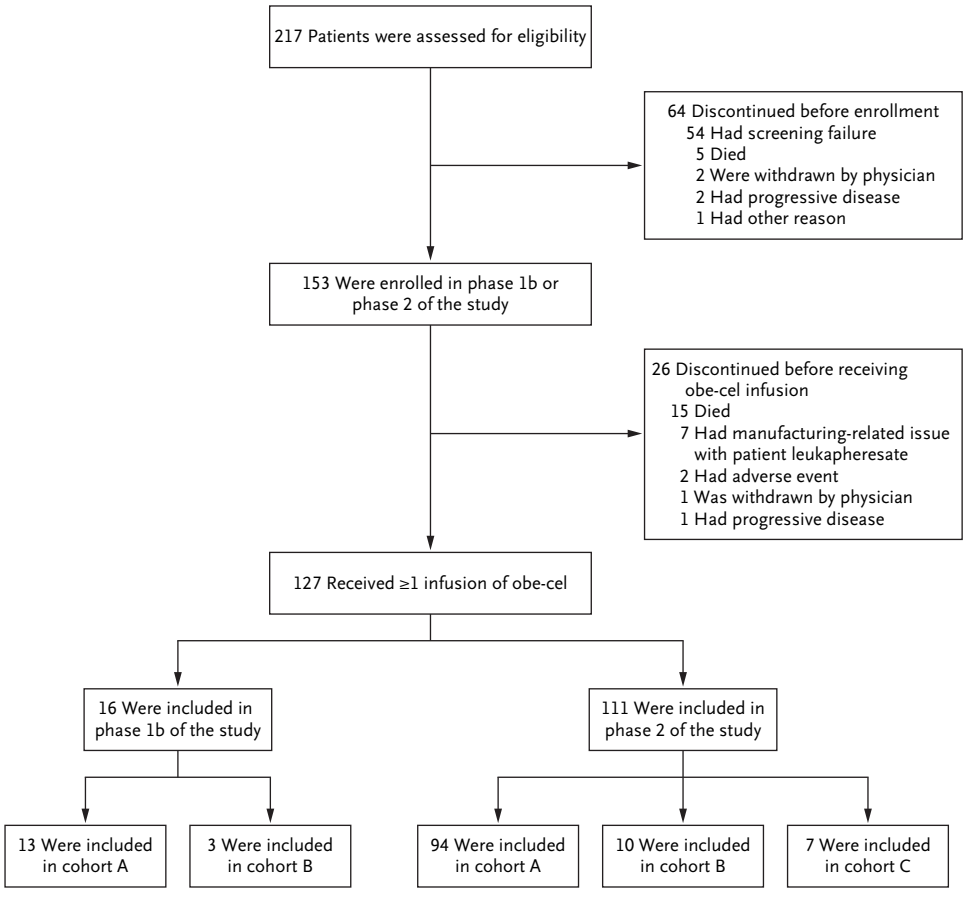


Figure 1. Screening, Enrollment, and Infusion.

Shown is the disposition of the entire study population. Enrolled patients had met all the inclusion criteria and none of the exclusion criteria and had leukapheresate sufficient for the manufacture of obe-cel. Cohort A included adults (≥18 years of age) with B-cell acute lymphoblastic leukemia (ALL) who had 5% or more bone marrow blasts at enrollment. Cohort B included adults with B-cell ALL who were in morphologic remission with measurable residual disease and had less than 5% bone marrow blasts at enrollment. Cohort C included adults with B-cell ALL who had isolated extramedullary disease at enrollment. Obe-cel denotes obecabtagene autoleucel.

Among all the patients who received at least one infusion, the median age was 47 years (range, 20 to 81), patients received a median of two previous lines of therapy (range, two to six), and 52.0% were refractory to their last line of therapy. Overall, 41.7% of the patients had previously received blinatumomab, 31.5% had received inotuzumab ozogamicin, and 16.5% had received both. A total of 56 patients (44.1%) had previously undergone an allogeneic stem-cell transplantation. Patients had a median of 40.0% bone marrow blasts (range, 0 to 100) at enrollment. A total of 29 patients (22.8%) had extramedullary disease, and 36 (28.3%) had Philadelphia chromosome–positive B-cell ALL. Further details of patient and disease characteristics are shown in Table S9.

BRIDGING THERAPY AND BONE MARROW BURDEN

Bridging therapy was administered to 118 of 127 patients (92.9%). A total of 80 of 127 patients (63.0%) received chemotherapy alone, 10 (7.9%) received chemotherapy plus a tyrosine kinase inhibitor, 9 (7.1%) received chemotherapy plus inotuzumab ozogamicin, 9 (7.1%) received inotuzumab ozogamicin alone, 7 (5.5%) received a

Table 1. Demographic and Disease Characteristics of the Patients before Enrollment.*

Characteristic	Cohort 2A Patients Who Received Infusion (N = 94)†	All the Patients Who Received Infusion (N = 127)‡
Demographic characteristics		
Age		
Median (range) — yr	50.0 (20–81)	47.0 (20–81)
≥65 yr — no. (%)	21 (22)	25 (20)
Sex — no. (%)		
Male	47 (50)	66 (52)
Female	47 (50)	61 (48)
Race — no. (%)§		
Asian	10 (11)	16 (13)
Black	2 (2)	2 (2)
White	70 (74)	94 (74)
Unknown	12 (13)	15 (12)
Hispanic or Latino ethnic group — no. (%)§		
Yes	29 (31)	38 (30)
No	58 (62)	80 (63)
Unknown	7 (7)	9 (7)
Previous therapies		
Median no. of previous lines of therapy (range)	2.0 (1–6)	2.0 (1–6)
Refractory to all previous lines of anticancer therapy — no. (%)	12 (13)	13 (10)
Refractory to first-line therapy — no. (%)	24 (26)	32 (25)
Had relapse within 12 mo after receipt of first-line therapy — no. (%)	41 (44)	60 (47)
Refractory to last previous line of therapy — no. (%)	51 (54)	66 (52)
Previous use of blinatumomab — no. (%)	33 (35)	53 (42)
Previous use of inotuzumab ozogamicin — no. (%)	30 (32)	40 (31)
Previous use of blinatumomab and inotuzumab ozogamicin — no. (%)	15 (16)	21 (17)
Previous allogeneic stem-cell transplantation — no. (%)	36 (38)	56 (44)
Disease characteristics		
Median percentage of bone marrow blasts (range) on morphologic analysis¶	58.9 (6–100)	40.0 (0–100)
Extramedullary disease — no. (%)	19 (20)	29 (23)
Philadelphia chromosome–positive disease — no. (%)	25 (27)	36 (28)
ECOG performance-status score — no. (%)‖		
0	35 (37)	50 (39)
1	58 (62)	76 (60)
CNS disease history — no. (%)		
CNS1**	81 (86)	112 (88)
CNS2††	2 (2)	3 (2)

* Percentages may not total 100 because of rounding. CNS denotes central nervous system.
† All the inclusion criteria and none of the exclusion criteria were fulfilled, and patient leukapheresate was sufficient for the manufacture of obecabtagene autoleucel (obe-cel).
‡ Shown are all the patients who received at least one infusion of obe-cel.
§ Race and ethnic group were reported by the patient.
¶ Shown is the highest value from bone marrow aspirate and trephine before enrollment.
‖ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Data were missing for one patient in each group.
** CNS1 indicates no lymphoblasts in cerebrospinal fluid regardless of the white-cell count.
†† CNS2 indicates a white-cell count of less than 5 per microliter in cerebrospinal fluid with the presence of lymphoblasts.

Table 2. Response According to Cohort and in All the Patients Who Received at Least One Infusion of Obe-Cel.*

Response	Phase 1b (N=16)		Phase 2 (N=111)			All the Patients Who Received Infusion (N=127)
	Cohort A (N=13)	Cohort B (N=3)	Cohort A (N=94)	Cohort B (N=10)	Cohort C (N=7)	
CR or CRi						
No. of patients	9	2	72	10	6	99
% (95% CI)	69 (39–91)	67 (9–99)	77 (67–85)	100 (69–100)	86 (42–100)	78 (70–85)
CR — no. (%)	6 (46)	2 (67)	52 (55)	9 (90)	4 (57)	73 (57)
CRi — no. (%)	3 (23)	0	20 (21)	1 (10)	2 (29)	26 (20)

* CR denotes complete remission, and CRi complete remission with incomplete hematologic recovery.

tyrosine kinase inhibitor alone, 2 (1.6%) received glucocorticoids alone, and 1 (0.8%) received rituximab alone (Table S10). Patients with a higher bone marrow burden at enrollment tended to have more intensive bridging therapy (Table S11).

Before lymphodepletion, all the patients underwent repeat bone marrow assessment; the median percentage of bone marrow blasts was 40.0% (range, 0 to 100), with less than 5% blasts in 28.3%, 5 to 20% blasts in 12.6%, and more than 20% blasts in 59.1%. A total of 27 patients (21.3%) had extramedullary disease. For most patients, the bone marrow burden changed between enrollment and lymphodepletion owing to bridging therapy (Fig. S4). For instance, 23 of 94 patients (24%) in cohort 2A (>5% bone marrow blasts at enrollment) had less than 5% bone marrow blasts before lymphodepletion. Consequently, a post hoc analysis of the entire FELIX study was performed and is described below.

OBE-CEL ADMINISTRATION

A total of 76 of 127 patients (59.8%) received 10×10^6 CAR T cells as dose 1, and 51 of 127 (40.2%) received 100×10^6 CAR T cells as dose 1. A total of 120 of 127 patients (94.5%) received both planned doses of obe-cel (Table S12). Seven of 127 patients (5.5%) received dose 1 only, owing to immunotoxic effects in 3 patients (grade 3 ICANS in 2 and grade 3 cytokine release syndrome in 1), death due to a cerebrovascular incident in 1, a manufacturing-related issue in 1, and rapid disease progression in 2 (Table S13). A total of 88 of 94 patients in cohort 2A (94%) received both doses.

RESPONSE AND SURVIVAL

Cohort 2A

The median follow-up in cohort 2A was 20.3 months. The incidence of overall remission among patients who received at least one infusion of obe-cel was 77% (95% confidence interval [CI], 67 to 85), of whom 55% (95% CI, 45 to 66) had complete remission and 21% (95% CI, 14 to 31) had complete remission with incomplete hematologic recovery. Both the prespecified null hypotheses of the overall-remission end point (≤40%) and the complete-remission end point (≤20%) were rejected, with P values of less than 0.001. The median response duration was 14.1 months (95% CI, 8.2 to not evaluable) (Fig. S5B). The median event-free survival was 9.0 months (95% CI, 6.1 to 15.0). Responses in all FELIX cohorts are summarized in Table 2.

All the Patients Who Received an Infusion

Of the 91 of 127 patients with 5% or more bone marrow blasts before lymphodepletion, 68 of 91 (75%; 95% CI, 64 to 83) had overall remission (complete remission or complete remission with incomplete hematologic recovery). A total of 62 of 68 patients with a response had MRD data available, and 58 of 62 (94%) were MRD-negative after obe-cel infusion. In the 29 patients with less than 5% bone marrow blasts without extramedullary disease before lymphodepletion, 27 of 28 (96%) with MRD data available had MRD-negative remission. Five of 7 patients (71%) with less than 5% blasts and extramedullary disease before lymphodepletion had clearance of extramedullary disease after obe-cel infusion.

A high incidence of overall remission was observed across all patient subgroups after obe-cel infusion (Fig. S6), but a lower incidence was observed among patients with a high bone marrow burden (>75% bone marrow blasts) than among those with an intermediate bone marrow burden (5 to 75% bone marrow blasts) before lymphodepletion (65% [95% CI, 48 to 79] vs. 82% [95% CI, 69 to 92]). The correlation between response and bone marrow blasts is shown in Figure S7.

Intention-to-Treat Population

Responses in the intention-to-treat population (153 patients) are summarized in Table S14. Among the 112 patients enrolled in cohort 2A, the incidence of overall remission was 64.3% (95% CI, 54.7 to 73.1); among the 153 patients enrolled in the FELIX study, the incidence was 64.7% (95% CI, 56.6 to 72.3).

Response Duration and Survival

The median duration of follow-up from the first obe-cel infusion to the data-cutoff date (February 7, 2024) in all the patients who received at least one infusion was 21.5 months (range, 8.6 to 41.4). The median response duration was 21.2 months (95% CI, 11.6 to not evaluable) (Fig. S5A).

The median event-free survival among all the patients who received at least one infusion was 11.9 months (95% CI, 8.0 to 22.1); the estimated 6- and 12-month event-free survival was 65.4% and 49.5%, respectively. Bone marrow burden before lymphodepletion correlated with event-free survival; patients with low (<5% bone marrow blasts), intermediate (5 to 75% blasts), and high (>75% blasts) bone marrow burden had event-free survival at 12 months of 68% (95% CI, 48 to 82), 55% (95% CI, 39 to 68), and 25% (95% CI, 12 to 41), respectively (Fig. 2A and 2B).

The median overall survival among all the patients who received at least one infusion was 15.6 months (95% CI, 12.9 to not evaluable), and the estimated 6- and 12-month overall survival was 80.3% and 61.1%, respectively. Bone marrow burden before lymphodepletion correlated with overall survival; patients with low, intermediate, and high bone marrow burden had an overall survival at 12 months of 72% (95% CI, 53 to 84), 59% (95% CI, 44 to 71), and 55% (95% CI, 38 to 69), respectively. (Fig. 2C and 2D). Bone marrow burden before enrollment also influenced event-free and overall survival (Fig. S8).

ALLOGENEIC STEM-CELL TRANSPLANTATION

Of the 99 patients in the intention-to-treat population who had a response, 18 (18%) proceeded to allogeneic stem-cell transplantation while in remission at a median of 101 days (range, 38 to 421) after obe-cel infusion. In 6 of 18 patients (33%), this procedure was a second allogeneic stem-cell transplantation. Of 11 patients who had persisting CAR T cells before allogeneic stem-cell transplantation and who had samples available afterward, none had CAR T cells detected after allogeneic stem-cell transplantation. No substantial difference in event-free or overall survival was observed between patients who received allogeneic stem-cell transplantation and those who did not (Fig. S9). Consolidation with a tyrosine kinase inhibitor (Fig. S10) and intrathecal chemotherapy are detailed in the Supplementary Results section.

RELAPSES

Of the 99 patients who had a response, 31 (31%) had a morphologic relapse by the data-cutoff date (Table S15). A morphologic relapse occurred in 6 of 31 patients (19%) with less than 5% bone marrow blasts at lymphodepletion, 12 of 42 (29%) with 5 to 75% bone marrow blasts, and 13 of 26 (50%) with more than 75% bone marrow blasts. Five patients had isolated extramedullary relapse, including 2 with central nervous system disease. In addition, 3 patients had a bone marrow relapse with concomitant extramedullary presentation at the time of relapse.

SAFETY

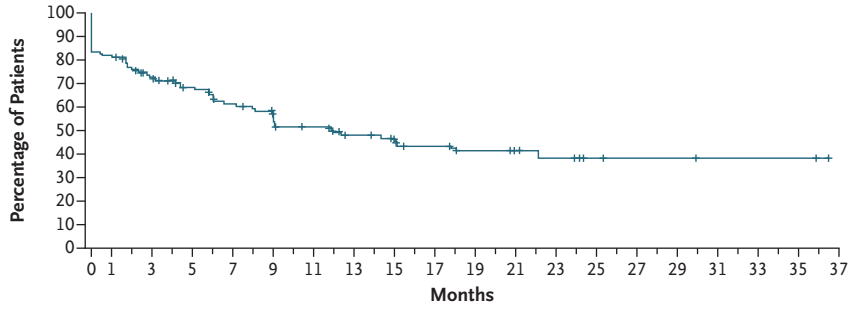
General

Immunotoxic effects, cytopenias, and infections are summarized in Table 3. Serious adverse events are shown in Table S16A, and all adverse events are shown in Table S16B.

Cytokine Release Syndrome

Cytokine release syndrome developed in 87 of 127 patients (68.5%), with events of grade 3 or higher in 3 patients (2.4%). The median time to onset of cytokine release syndrome was 8 days (range, 1 to 23) after infusion, and the median

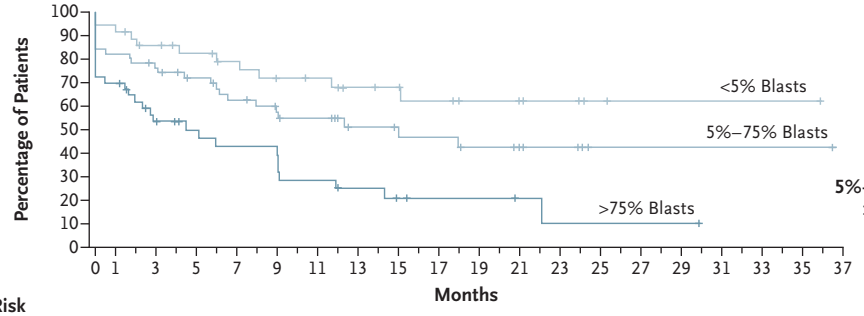
A Event-free Survival



No. at Risk																				
	127	104	85	70	60	53	46	33	28	25	21	15	12	5	3	3	2	2	2	0

	No. of Events	Median Event-free Survival (95% CI) *mo*
All Patients	63	11.9 (8.0–22.1)

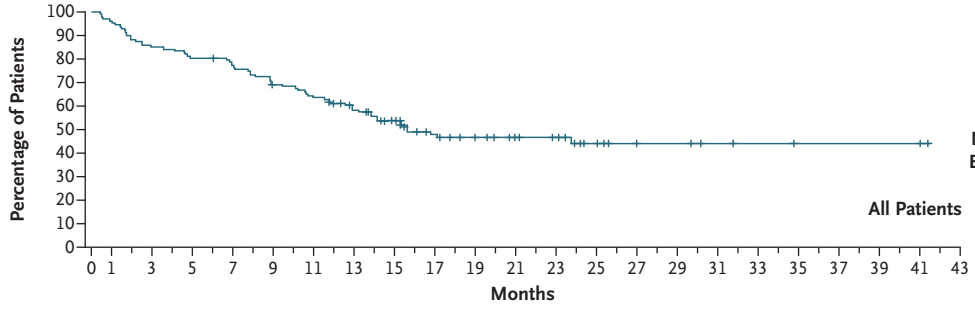
B Event-free Survival According to Bone Marrow Burden before Lymphodepletion



No. at Risk																				
<5% Blasts	36	34	28	25	22	19	18	14	13	11	9	7	6	3	1	1	1	1	1	0
5%–75% Blasts	51	42	38	31	26	22	20	13	11	11	9	6	5	1	1	1	1	1	1	0
>75% Blasts	40	28	19	14	12	12	8	6	4	3	3	2	1	1	1	1	0	0	0	0

	No. of Events	Median Event-free Survival (95% CI) *mo*
<5% Blasts	11	NE
5%–75% Blasts	24	15.0 (6.1–NE)
>75% Blasts	28	5.1 (1.6–9.0)

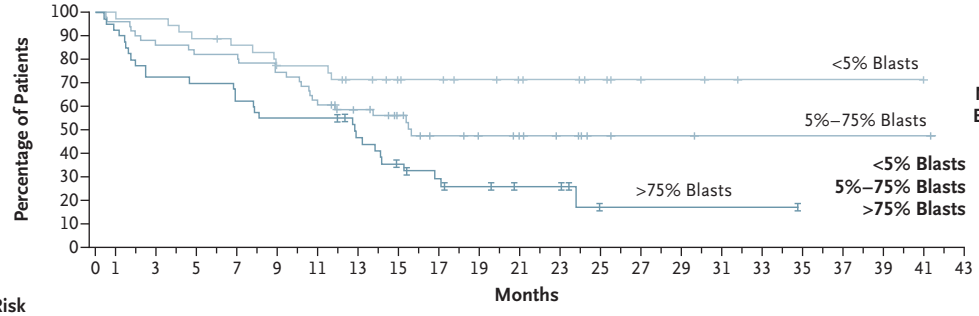
C Overall Survival



No. at Risk																				
	127	122	108	102	97	86	79	64	51	39	32	25	21	12	7	6	4	3	2	2	2	2	0

	No. of Events	Median Overall Survival (95% CI) *mo*
All Patients	64	15.6 (12.9–NE)

D Overall Survival According to Bone Marrow Burden before Lymphodepletion



No. at Risk																							
<5% Blasts	36	36	35	32	30	26	26	21	18	16	13	10	9	6	4	3	2	1	1	1	1	1	0
5%–75% Blasts	51	49	44	42	42	38	31	26	21	14	12	10	7	4	2	2	1	1	1	1	1	1	0
>75% Blasts	40	37	29	28	25	22	22	17	12	9	7	5	5	2	1	1	1	1	0	0	0	0	0

	No. of Events	Median Overall Survival (95% CI) *mo*
<5% Blasts	10	NE
5%–75% Blasts	25	15.6 (10.6–NE)
>75% Blasts	29	12.8 (6.9–15.3)

Figure 2 (facing page). Event-free and Overall Survival.
Panel A shows event-free survival among all the patients who received at least one infusion of obe-cel, Panel B event-free survival among all the patients who received at least one infusion according to bone marrow burden before lymphodepletion, Panel C overall survival among all the patients who received at least one infusion, and Panel D overall survival among all the patients who received at least one infusion according to bone marrow burden before lymphodepletion. NE denotes not evaluable.

duration was 5 days (range, 1 to 21). Tocilizumab was administered to 66 patients (52.0%), and glucocorticoids were administered to 20 (15.7%). Three patients (2.4%) received vasopressors, and 15 (11.8%) received supplemental oxygen. Immune effector cell–associated hemophagocytic lymphohistiocytosis affected 2 patients, and both events were of grade 3 or higher.

ICANS

ICANS developed in 29 of 127 patients (22.8%), with events of grade 3 or higher in 9 patients (7.1%). The median time to onset of ICANS was 12 days (range, 1 to 31) after infusion, and the median duration was 8 days (range, 1 to 53). Of 29 patients with ICANS, 24 received glucocorticoids. Grade 3 or higher ICANS developed in 9 patients. Of these 9 patients, 5 (56%) had more than 75% bone marrow blasts before lymphodepletion and 4 (44%) had 5 to 75% bone marrow blasts; grade 3 or higher ICANS developed in no patients with less than 5% bone marrow blasts before lymphodepletion.

Biomarkers

Serum biomarkers are shown in Figure S11. After infusion, the median peak interferon-γ level was 12.9 ng per liter (range, 7.0 to 30.9), and the median peak interleukin-6 level was 3.4 ng per liter (range, 1.7 to 8.0). Peak cytokine levels were higher in patients with cytokine release syndrome and, to a lesser extent, in patients with ICANS than in those without these conditions.

Cytopenias

Among the 99 patients with overall remission after obe-cel infusion, the median time from the day of infusion to neutrophil recovery ($\geq 0.5\times10^9$ per liter) was 21 days (95% CI, 15 to 27), and the median time to platelet-count recovery ($\geq 50\times10^9$ per liter) was 21 days (95% CI, 9 to 52). Preexisting cytopenia was associated with a longer duration of cytopenia (Fig. S12). All the patients had neutrophil recovery before month 6, and 2 patients had platelet-count recovery that took longer than 6 months. Allogeneic donor stem cells were administered to 1 patient with overall remission who had prolonged cytopenia.

Infections

In the 60 days after obe-cel infusion, febrile neutropenia occurred in 31 of 127 patients (24.4%), with five deaths from infections: two from neutropenic sepsis (one related and one not related to obe-cel), two from sepsis (not related to obe-cel), and one from abdominal infection (not related to obe-cel). A total of 50 patients (39.4%) received intravenous immune globulin after obe-cel infusion.

Admissions to Intensive Care Unit

Overall, 20 of 127 patients (15.7%) were admitted to an intensive care unit for a median of 5.5 days (range, 1 to 37). Seven of the 20 patients were admitted for the management of immunotoxic effects (5 patients with ICANS and 2 with cytokine release syndrome).

Deaths

Deaths are detailed in Table S17. In two patients, death was attributable to obe-cel: one patient died of acute respiratory distress syndrome with ongoing ICANS, and one died of neutropenic sepsis.

CAR T-Cell Engraftment and Relapse

The geometric mean peak CAR T-cell concentration in all the patients who received at least one obe-cel infusion was 110,896 copies per microgram of genomic DNA (range, 129 to 600,000) (see the Supplementary Results section and Fig. S13). A higher maximum concentration and a higher area under the curve within the first 28 days after infusion were associated with a higher incidence of cytokine release syndrome or ICANS (Fig. S14) but not with a higher incidence of overall remission (Fig. S15). The median duration of CAR T-cell persistence in peripheral blood as assessed by droplet digital polymerase-chain-reaction assay was 17.8 months (95% CI, 6.2 to not evaluable) (Fig. S16A). The probability of ongoing B-cell aplasia was 80.7% (95% CI,

Table 3. Summary of Adverse Events of Special Interest.*

Event	<5% Blasts (N=36)		5–75% Blasts (N=51)		>75% Blasts (N=40)		All the Patients Who Received Infusion (N=127)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)							
Cytokine release syndrome	17 (47)	0	36 (71)	2 (4)	34 (85)	1 (2)	87 (69)	3 (2)
ICANS	3 (8)	0	10 (20)	4 (8)	16 (40)	5 (12)	29 (23)	9 (7)
Febrile neutropenia	—	—	—	—	—	—	31 (24)	30 (24)
Infections and infestations	—	—	—	—	—	—	99 (78)	66 (52)

* Cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome (ICANS) are shown for all the patients who received at least one infusion of obe-cel and according to bone marrow burden before lymphodepletion. Febrile neutropenia and infections are shown for all the patients who received at least one infusion of obe-cel.

70.3 to 87.8) at 6 months and 66.7% (95% CI, 53.9 to 76.7) at 12 months (Fig. S16B).

Among 31 patients whose expression of CD19 in blasts was assessed at the time of relapse, most (9 of 11; 82%) with ongoing CAR T-cell persistence had a relapse with CD19-negative blasts, whereas most (14 of 20; 70%) without persistence had a relapse with CD19-positive or mixed blasts (Table S15). In the 2 patients who had a relapse with persisting CAR T cells and CD19-positive blasts, levels of CAR T-cell persistence did not increase on relapse.

DISCUSSION

In the FELIX study, obe-cel was administered to 127 patients with relapsed or refractory B-cell ALL. Formal hypothesis testing was performed for the primary end point of overall remission (complete remission or complete remission with incomplete hematologic recovery) and the key secondary end point of complete remission in cohort 2A. Other descriptive analyses were also performed. Among the 94 patients in the pivotal 2A cohort, the incidence of overall remission was 77%. Among all the patients, the median event-free survival was 11.9 months, with estimated 6- and 12-month event-free survival of 65.4% and 49.5%, respectively. Obe-cel was associated with a low incidence of grade 3 or higher immunotoxic effects, with grade 3 or higher cytokine release syndrome in 2.4% of the patients and grade 3 or higher ICANS in 7.1%.

Although blinatumomab[12] and inotuzumab ozogamicin[13] have been shown to increase the likelihood of response in patients with relapsed or refractory B-cell ALL, consolidation with allogeneic stem-cell transplantation is needed for durable response. Recently, the CD28-ζ CD19 CAR T-cell therapeutic brexu-cel was licensed for adults 18 years of age or older with relapsed or refractory B-cell ALL.[4-6] Although the incidence of overall remission was 71%,[6] brexu-cel was associated with a much higher incidence of grade 3 or higher cytokine release syndrome (24 to 26%, as compared with 2.4% with obe-cel), grade 3 or higher ICANS (25 to 35%, as compared with 7.1% with obe-cel),[6,14] and vasopressor use (40%, as compared with 2.4% with obe-cel).[6] Indeed, severe ICANS after obe-cel infusion was largely limited to patients with a high bone marrow burden before lymphodepletion, which suggests that obe-cel may be safely administered in an ambulatory setting in patients with a low bone marrow burden.

In the entire study population, 12-month event-free and overall survival estimates were 49.5% and 61.1%, respectively. Patients with a low bone marrow burden (<5% blasts) or intermediate bone marrow burden (5 to 75% blasts) before lymphodepletion had better event-free survival results than those with a high bone marrow burden (>75% blasts), which suggests that low-to-intermediate bone marrow burden is optimal for CAR T-cell efficacy and toxicity and that optimized bridging therapy approaches toward better tumor clearance before CAR T-cell therapy may improve outcomes. Furthermore,

obe-cel as earlier-line consolidation, particularly in the context of MRD, deserves further exploration.

In the FELIX study, obe-cel resulted in a high incidence of response among adults with relapsed or refractory B-cell ALL, with toxic effects mostly limited to patients with a high bone marrow burden. Furthermore, obe-cel was associated with durable responses, particularly in patients with a low-to-intermediate bone marrow burden, including patients who did not receive consolidative allogeneic stem-cell transplantation.

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APPENDIX

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