Tumor burden-guided dosing contributes to mitigation of immunotoxicities following treatment with obecabtagene autoleucel in adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia

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Supplementary Appendix

Tumor burden-guided dosing contributes to mitigation of immunotoxicities following treatment with obecabtagene autoleucel in adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia

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Administration in practice

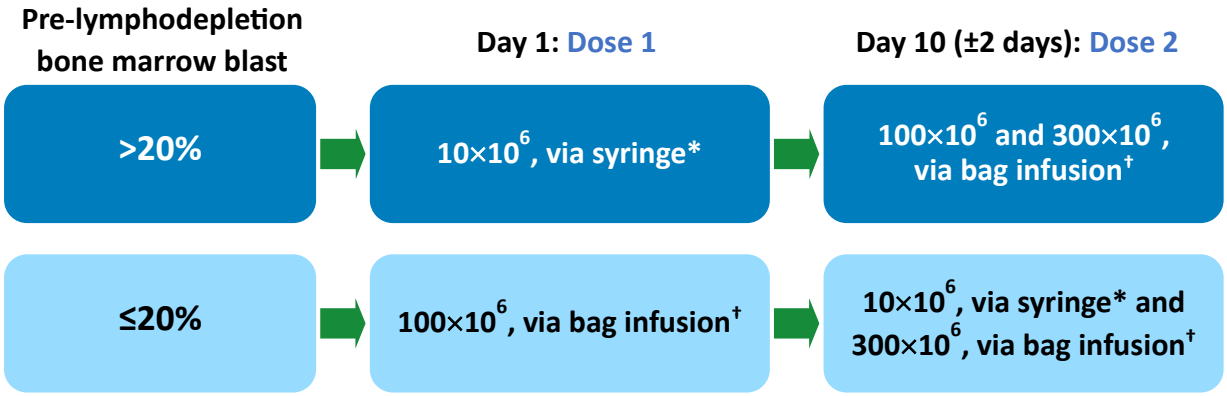
Administration in practice: AUCATZYL® (obecabtagene autoleucel [obe-cel]) suspension for intravenous infusion[1]

Obe-cel is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

Dosage and administration

- Obe-cel is a cell suspension for infusion and intended for autologous and intravenous use only.
- The total recommended dose of obe-cel is 410×10^6 CD19 chimeric antigen receptor (CAR)-positive viable T cells supplied in three to five infusion bags (10×10^6, 100×10^6, 300×10^6) for split dose administration.
- A bone marrow assessment must be available from a sample obtained within 7 days prior to the commencement of lymphodepleting chemotherapy treatment.
- The bone marrow assessment will be used to determine the dosage regimen based on a bone marrow blast of >20% or ≤20%.
- If the bone marrow assessment results are inconclusive, repeat the biopsy or aspirate (only if lymphodepleting chemotherapy treatment has not started).
- If results remain inconclusive, proceed with the bone marrow blast of >20% dosage.
- Administer the lymphodepleting chemotherapy regimen before infusion of obe-cel: fludarabine (FLU) 30 mg/m^2/day intravenously for 4 days and cyclophosphamide (CY) 500 mg/m^2/day intravenously for 2 days starting with the first dose of fludarabine (total dose: FLU 120 mg/m^2; CY 1,000 mg/m^2). Infuse obe-cel 3 days (± 1 days) after completion of lymphodepleting chemotherapy treatment (Day 1), allowing a minimum 48-hour washout.
- To minimize the risk of an infusion reaction, premedicate with acetaminophen approximately 30 minutes prior to obe-cel infusion.

- Confirm availability of tocilizumab prior to infusion for the potential treatment of cytokine release syndrome (CRS).
- Avoid prophylactic use of systemic corticosteroids as they may interfere with the activity of obe-cel.
- Proceed with obe-cel administration as outlined below:



*Volume specified per infusion bag, calculated based on the concentration of CD19 CAR-positive viable T cells, administer at a rate of 0.5mL/minute through a central venous line or large peripheral venous access line. †Administer the full content of the bag via a gravity or peristaltic pump assisted intravenous infusion through a central venous line or large peripheral venous access line at a rate of 0.1–27mL/minute.

- Monitor patients for signs and symptoms of CRS, neurologic toxicities/immune effector cell-associated neurotoxicity syndrome (ICANS) and other acute toxicities daily for at least 14 days at the healthcare facility following the first infusion.
- Continue to monitor patients for at least 4 weeks following each infusion.
- Discontinue treatment if, patients develop grade ≥3 CRS and/or grade ≥2 ICANS or grade ≥3 pulmonary or cardiac toxicities following the Dose 1. Dose 2 infusion for patients who develop maximum grade 2 CRS and/or grade 1 ICANS following infusion of Dose 1 may be delayed up to day 21, and administered only if CRS resolves to grade ≤1 and ICANS completely resolves.

Supplementary Materials and Methods

The design and conduct of the FELIX study was previously reported.[2]

Treatment/dosing schedule

Following leukapheresis, patients received bridging therapy at the discretion of the investigator to reduce the percentage of bone marrow blasts prior to lymphodepletion. Bone marrow blast percentage was assessed locally within 7 days prior to lymphodepletion and assessed by centralized morphologic review to determine tumor burden. Obe-cel was administered according to a tumor burden-guided dosing schedule following lymphodepletion with fludarabine and cyclophosphamide. The study design allowed for the treatment of adverse events prior to the administration of the second dose of obe-cel.

Tocilizumab was recommended for the treatment of grade ≥2 CRS as a 60-minute intravenous infusion (8 mg/kg in patients weighing ≥30 kg or 12 mg/kg in patients weighing <30 kg); a maximum of 800 mg per infusion was recommended. If no clinical improvement occurred following the first dose, up to three additional doses of tocilizumab were permitted with an interval of at least 8 hours between doses. Corticosteroids were recommended for the treatment of grade 3 CRS refractory to tocilizumab, grade 4 CRS, and grade ≥2 ICANS (recommended dose of methylprednisolone of 2 mg/kg intravenously every 12 hours over 5 days, and dexamethasone of 10 mg intravenously every 6 hours).

Assessments and endpoints

Serum cytokine levels were measured using peripheral blood samples collected pre-lymphodepletion and on days 1, 3, 6, 9, 12, 15, 22, and 28, and month 3 post obe-cel infusion. Post obe-cel infusion response/relapse was monitored at day 28, months 2, 3, 4, 6, and every 3 months thereafter until the end of study based on peripheral blood and/or BM assessments.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) 26.0 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. CRS and ICANS were graded using the American Society for Transplantation and Cellular Therapy (ASTCT)/American Society for Blood and Marrow Transplantation (ASBMT) consensus guidelines.[3]

Statistical analyses

Statistical analyses for the comparison of efficacy outcomes and pharmacokinetic parameters between subgroups based on patient and disease characteristics were not performed, as these were not pre-specified endpoints in the trial.

Supplementary results

Supplementary Table 1. Baseline characteristics of the infused set of patients (N=127).

	Low TB (N=52)	**High TB (N=75)**
Age in years, median (range)	44 (20-81)	49 (20-79)
Male/female sex, N	28/24	38/37
Race, N (%)		
Asian	8 (15)	8 (11)
Black or African American	0 (0)	2 (3)
White	41 (79)	53 (71)
Unknown	3 (6)	12 (16)
Ethnicity, N (%)		
Hispanic or Latino	11 (21)	27 (36)
Not Hispanic or Latino	37 (71)	43 (57)
Unknown	4 (8)	5 (7)
Philadelphia chromosome-positive, N (%)	17 (33)	19 (25)
Philadelphia chromosome-like disease, N (%)	4 (8)	6 (8)
Prior lines of therapy, median (range)	2 (1-5)	2 (1-6)
≥3 prior lines, n (%)	22 (42)	23 (31)
Refractory to all prior lines of therapy, N (%)	3 (6)	10 (13)
Refractory to first-line therapy, N (%)	10 (19)	22 (29)
Refractory to last prior line of therapy, N (%)	27 (52)	39 (52)
Prior blinatumomab, N (%)*	20 (38)	33 (44)
Prior inotuzumab ozogamicin, N (%)*	16 (31)	24 (32)
Prior blinatumomab or inotuzumab ozogamicin, N (%)*	27 (52)	45 (60)
Prior blinatumomab and inotuzumab ozogamicin, N (%)*	9 (17)	12 (16)
Prior allo-SCT, N (%)	30 (58)	26 (35)

TB (BM blast %) at screening, median (range)	25 (0-100)	47 (0-100)
TB (BM blast %) at lymphodepletion, median (range)	2 (0-20)	80 (26-100)
Extramedullary disease at screening, N (%)	13 (25)	16 (21)

*Therapies administered prior to screening.

Low TB refers to patients with ≤20% BM blasts at lymphodepletion and high TB refers to patients with >20% BM blasts at lymphodepletion. allo-SCT: allogeneic stem cell transplant;

BM: bone marrow; TB: tumor burden.

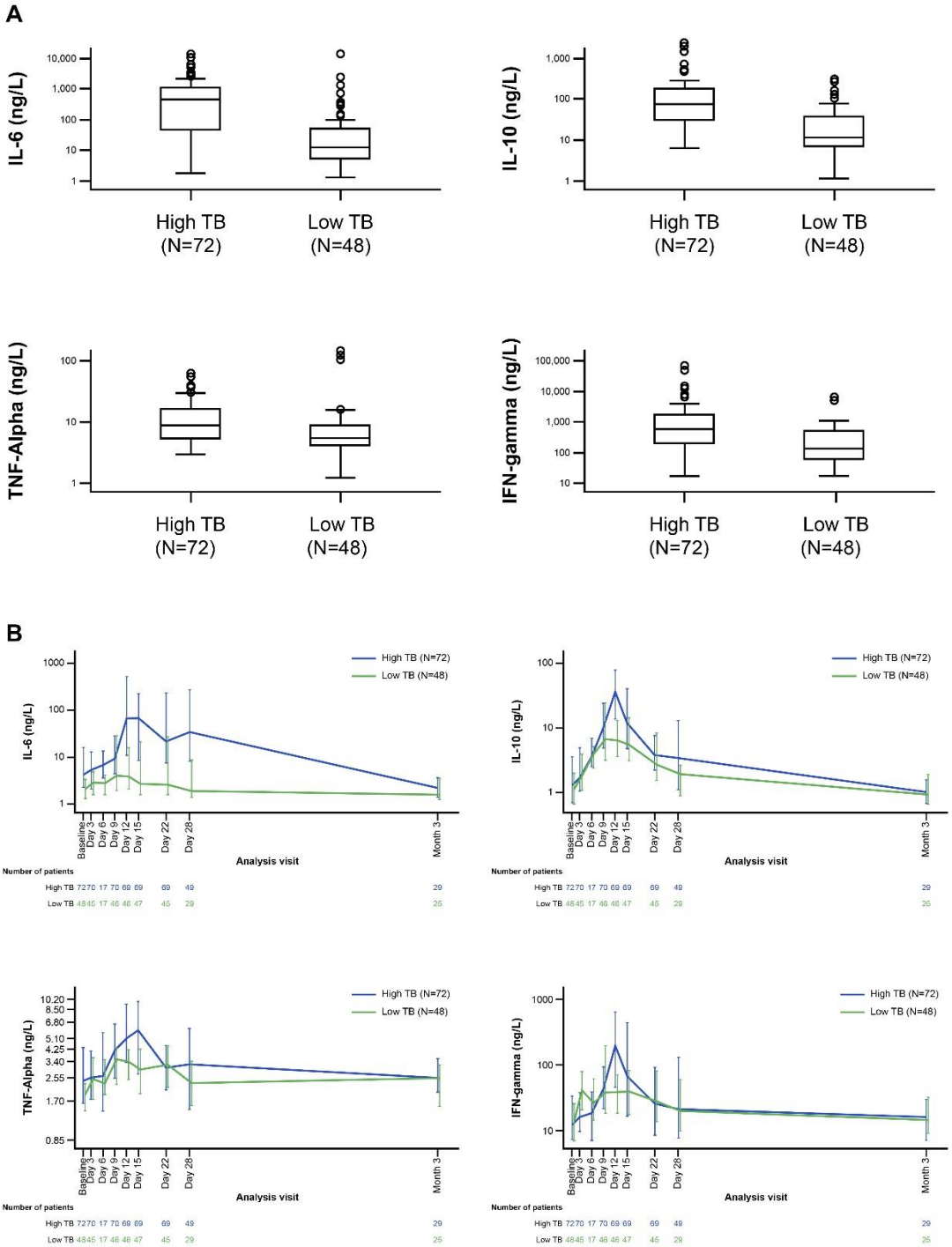
Supplementary Table 2. Characteristics and outcomes for patients who received only one dose of obe-cel.

Patient	% BM blasts at lymphodepletion	EMD 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	Yes	10×10^6	Grade 3 ICANS	No CR/CRi	245,000
2	98	No	10×10^6	Progressive disease	No CR/CRi	NE
3	99	No	10×10^6	Death due to cerebrovascular incident at day 14	No CR/CRi	308,000
4	30	No	10×10^6	Grade 3 CRS	CRi	288,000
5	80	Yes	10×10^6	Grade 3 ICANS	No CR/CRi	490,000
6	0	No	100×10^6	Low dose manufactured	CRi	10,900
7	10	No	100×10^6	Progressive disease	No CR/CRi	3,010

Table adapted from Roddie C et al. N Engl J Med. 2024;391(23):2219-2230 (Supplementary Appendix)[2] to include additional relevant data.

BM: bone marrow; CAR: chimeric antigen receptor; C_{max}: maximal expansion of transgene/chimeric antigen receptor-positive T-cell levels post-infusion; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; CRS: cytokine release syndrome; EMD: extramedullary disease; ICANS: immune effector cell-associated neurotoxicity syndrome; NE: not estimable; obe-cel: obecabtagene autoleucel.

Supplementary Figure 1. Interleukin-6, interleukin-10, tumor necrosis factor alpha, and interferon-gamma levels in patients who received both doses obe-cel (N=120). (A) Peak levels by tumor burden group. (B) Levels by visit. Low TB refers to patients with ≤20% BM blasts at lymphodepletion and high TB refers to patients with >20% BM blasts at lymphodepletion. BM: bone marrow; TB: tumor burden.



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