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clinical trial updates

Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

In the primary analysis of the global phase II ELIANA trial (ClinicalTrials.gov identifier: NCT02435849), tisagenlecleucel provided an overall remission rate of 81% in pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL), with 59% of responders remaining relapse-free at 12 months. Here, we report an update on efficacy, safety, and patient-reported quality of life in 79 pediatric and young adult patients with R/R B-ALL following a median follow-up of 38.8 months. The overall remission rate was 82%. The median event-free survival was 24 months, and the median overall survival was not reached. Event-free survival was 44% (95% CI, 31 to 57) and overall survival was 63% (95% CI, 51 to 73) at 3 years overall (most events occur within the first 2 years). The estimated 3-year relapse-free survival with and without censoring for subsequent therapy was 52% (95% CI, 37 to 66) and 48% (95% CI, 34 to 60), respectively. No new or unexpected long-term adverse events were reported. Grade 3/4 adverse events were reported in 29% of patients > 1 year after infusion; grade 3/4 infection rate did not increase > 1 year after infusion. Patients reported improvements in quality of life up to 36 months after infusion. These findings demonstrate favorable long-term safety and suggest tisagenlecleucel as a curative treatment option for heavily pretreated pediatric and young adult patients with R/R B-ALL.

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ASSOCIATED CONTENT

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Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) experience increased risk of morbidity with each additional line of salvage therapy.[1] Tisagenlecleucel is a CD19-directed chimeric antigen receptor (CAR) T–cell therapy[2] approved for use in pediatric and young adults with R/R B-ALL and adults with R/R diffuse large B-cell lymphoma and R/R follicular lymphoma.[3] In the primary analysis of the phase II ELIANA trial (ClinicalTrials.gov identifier: NCT02435849), tisagenlecleucel induced high remission rates (81%) in pediatric and young adults with R/R B-ALL.[4] Furthermore, most adverse events (AEs) occurred during the first 8 weeks after infusion,[4,5] and patients experienced significant quality-of-life (QOL) improvements.[6]

Given the high response rates, tisagenlecleucel has become the treatment of choice for many pediatric and young adult patients with R/R B-ALL. Herein, we report on the durability of response and potential for cure, long-term safety, and post–CAR-T cell therapy disease management on the basis of > 3 years of follow-up data from the ELIANA trial.

METHODS

Trial Design

ELIANA was a pivotal, phase II, open-label, multicenter, global study of tisagenlecleucel in pediatric and young adult patients with R/R B-ALL.[2] Trial design details and outcome measures have been previously published.[4,6] The median time from infusion to data cutoff reported here was 38.8 months. All patients provided written informed consent, and the study

received ethics approval by local institutional review boards at each participating institution.

RESULTS

Baseline Characteristics

Between April 8, 2015, and July 1, 2019, 97 patients were enrolled and 79 (81%) received tisagenlecleucel, including five additional enrollments after the previously reported primary analysis.[4] Patient demographics and clinical characteristics are shown in Table 1.

Efficacy

The published primary analysis (N = 75; median follow-up of 13.1 months) reported an overall remission rate (ORR) of 81% (95% CI, 71 to 89).[4] In the current updated analysis (N = 79; median follow-up of 38.8 months from the date of infusion to data cutoff), the ORR was 82% within 3 months (65/79; 95% CI, 72 to 90; Data Supplement, online only). Among the 66 patients who achieved complete response/complete remission with incomplete hematologic recovery, the median duration of remission (DOR) has not been reached (Fig 1A). The estimated relapse-free survival (RFS) rate (censored for allogeneic stem-cell transplant [alloSCT] and/or further anticancer therapies) was 58% (95% CI, 43 to 70) at 24 months and 52% at 36 months (95% CI, 37 to 66); the estimated RFS rate without censoring was 52.3% (95% CI, 39 to 64) at 24 months and 47.8% (95% CI, 34.4 to 60) at 36 months. Among responders who received no subsequent therapy while in complete remission (n = 32), the estimated RFS rate was 81% (95% CI, 62 to 91) at 24 months and 76% (95% CI, 56 to 88) at 36 months.

The median event-free survival (EFS) among all infused patients was 24 months (95% CI, 9.2 to not reached; Fig 1B) and the median EFS among responders (n = 66) has not been reached (95% CI, 18.7 to not reached; Data Supplement). The estimated EFS among all infused patients was 44% (95% CI, 31 to 57) at 36 months. A total of 24 events (all relapses) were recorded, of which six (25%) occurred > 12 months after infusion; the latest occurrence of relapse occurred 33 months after remission (Data Supplement). The median overall survival (OS) among all infused patients has not been reached, and the estimated OS rate was 63% (95% CI, 51 to 73; Fig 1C) at 36 months. Efficacy by baseline tumor burden is included in the Data Supplement.

We also examined the disease status and responses of patients who underwent alloSCT during the follow-up period. Twenty-two percent of patients (17/79) underwent alloSCT (Data Supplement); 11 were in tisagenlecleucel-mediated remission and, with a median of 18 months after alloSCT follow-up, none of these patients with available data (n = 8) relapsed. Additional details of supplemental therapy use are included in the Data Supplement.

TABLE 1. Patient Demographics and Clinical Characteristics

Characteristic	All Patients (N = 79)	Post-Infusion alloSCT (n = 17)	No Post-Infusion alloSCT (n = 62)
Age, years, median (range)	11 (3-24)	9 (4-21)	12 (3-24)
Sex, male, No. (%)	45 (57)	13 (77)	32 (52)
Prior HSCT, No. (%)	48 (61)	6 (35)	42 (68)
Previous lines of therapy, No., median (range)	3 (1-8)	2 (2-4)	3 (1-8)
Disease status, No. (%)			
Primary refractory	6 (8)	1 (6)	5 (8)
Relapsed	73 (92)	16 (94)	57 (92)
Morphologic blast count in bone marrow, %, median (range)[a]	74 (5-99)	84 (9-99)	72 (5-96)
CNS status classification, No. (%)			
CNS-1[b]	68 (86)	16 (88)	52 (84)
CNS-2	10 (13)	1 (6)	9 (15)
Unknown	1 (1)	0	1 (2)
High-risk genomic lesions,[c] No. (%)	30 (38)	9 (53)	21 (34)
Down syndrome, No. (%)	6 (8)	1 (6)	5 (8)

NOTE. Baseline demographics, clinical characteristics, and serum biomarkers constitute the last nonmissing observation prior to tisagenlecleucel infusion. Baseline is defined as the most current assessment on or prior to the date of enrollment.

Abbreviations: alloSCT, allogeneic stem cell transplant; HSCT, hematopoietic stem cell transplant.

[a]Morphologic blast count in bone marrow is the maximum from biopsy or aspirate prior to enrollment.

[b]One patient was CNS-1 prior to infusion and subsequently CNS-3 by unscheduled assessment on day 13 post infusion.

[c]BCR-ABL1, MLL rearrangement, hypoploidy, lesions associated with BCR-ABL1–like gene signature, or complex karyotype (≥ 5 unrelated abnormalities).

B-Cell Recovery and Chimeric Antigen Receptor Persistence

Median time to B-cell recovery among responders was 35.3 months (95% CI, 22.9 to not estimable; Data Supplement) and the probability of persistent B-cell aplasia at 12 and 24 months after infusion was 71% (95% CI, 57.4 to 81.5) and 59% (95% CI, 43.2 to 71.2), respectively. Among patients with sustained B-cell aplasia, the median DOR was 28 months (n = 50; Fig 2). The median DOR censored for alloSCT in patients with onset of B-cell recovery < 6 months after infusion was 12.1 months (n = 10) and has not been reached in patients with onset of B-cell recovery at 6 to 12 months (n = 2) and > 12 months (n = 4).

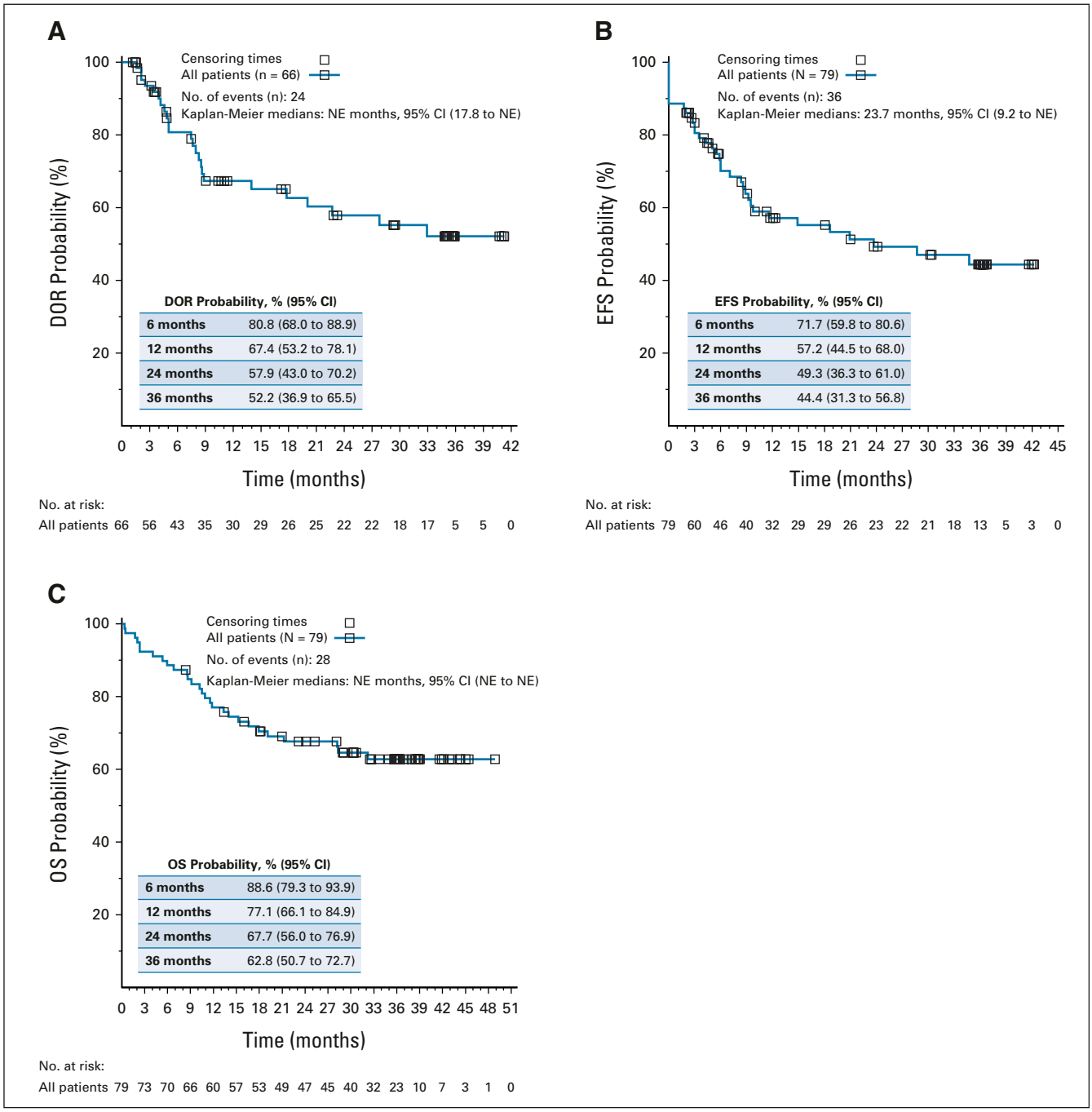

FIG 1. (A) DOR, (B) EFS, and (C) OS. (A) DOR—patients who achieved a BOR of CR/CRi are included. One patient who achieved a BOR of CRi within 6 months (day 173) is included. Time is relative to detection of remission. (B) EFS—time is relative to first tisagenlecleucel infusion date. (C) OS—time is relative to first tisagenlecleucel infusion date. BOR, best overall response; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission; EFS, event-free survival; NE, not estimable; OS, overall survival.

Safety

The safety profile of tisagenlecleucel observed in this long-term follow-up analysis was consistent with published reports,[4,5] and no new AEs or treatment-related mortality were observed (Data Supplement). The proportion of patients with grade 3/4 AEs declined over time (83.5% of patients < 8 weeks after infusion, 49% from 8 weeks to 1 year, and 29% > 1 year). The most frequent grade 3/4 AEs occurring > 1 year after infusion (n = 49) were infections (20.4%) and skin disorders (6.1%; all grade 3). Details of intravenous immunoglobulin use and hypogammaglobulinemia are provided in the Data Supplement.

Forty-six responding patients had both Pediatric Quality-of-Life Inventory and European Quality-of-Life-5 Dimensions questionnaire visual analog scale (EQ-5D VAS) assessments at baseline and at least one postbaseline visit. The clinically

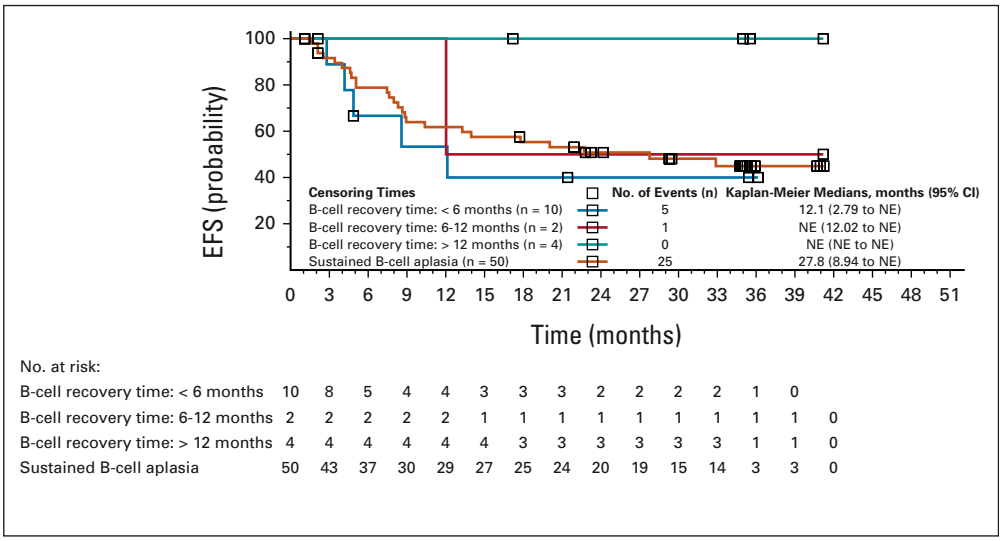

FIG 2. Duration of remission by B-cell recovery time point. Time is relative to first tisagenlecleucel infusion date. EFS, event-free survival; NE, not estimable.

meaningful improvement in health-related QOL that began as early as 3 months after infusion[6] continued to improve through the subsequent 36 months (Data Supplement). In general, the proportions of patients achieving the normative mean during the postbaseline period were greater than those at baseline even when patients with missing data were assumed to not achieve the normative mean (Data Supplement).

DISCUSSION

To our knowledge, tisagenlecleucel is the only CAR-T cell therapy to be approved for pediatric and young adult patients with R/R B-ALL. The data presented here, on the basis of a median follow-up of > 3 years, demonstrate durable efficacy with tisagenlecleucel in this heavily pretreated pediatric and young adult R/R B-ALL patients, with a 36-month RFS, EFS, and OS of 52%, 44%, and 63%, respectively.

The majority of responding patients did not undergo consolidative alloSCT. Although there were no reported relapses in patients following alloSCT in tisagenlecleucel-mediated remission, larger real-world studies are needed to assess the effect of alloSCT following CAR-T cell therapy because it is not possible to directly compare the survival outcomes of those who underwent transplant with those who did not because of the small patient number and biased selection of patients for transplant.

No new safety signals were identified in this analysis, with most AEs occurring within 8 weeks after infusion. Furthermore, long-term safety-related factors, such as hypogammaglobulinemia, intravenous immunoglobulin, and infection, do not appear to diminish the clinically meaningful improvements in QOL, which are maintained up to 36 months after infusion.

The current analysis supports the recently published finding that B-cell recovery within the first 6 months after infusion predicts risk of relapse and may be an indicator for clinicians to consider subsequent therapy[7]; however, B-cell recovery does not always precede relapse. In addition, several studies have demonstrated that high disease burden immediately before infusion is associated with an increased risk of nonresponse and early relapse.[8-10] It was not possible to explore this hypothesis because disease burden in ELIANA was only assessed before enrollment. All subjects were required to have ≥ 5% bone marrow blasts at that time but may have had a decrease before infusion. We eagerly await additional data on the effect of emerging preinfusion prognostic factors that will further inform clinical decision making, including disease burden and nonresponse to blinatumomab from the real-world setting. In conclusion, this > 3-year follow-up confirms the durable responses and manageable safety profile of tisagenlecleucel and demonstrates its curative potential in pediatric and young adult patients with R/R B-ALL.

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