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blood advances

Indirect comparison of tisagenlecleucel and blinatumomab in pediatric relapsed/refractory acute lymphoblastic leukemia

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Key points

- This study provides the first patient-level data indirect comparison of tisagenlecleucel vs blinatumomab in R/R ALL.
- Tisagenlecleucel was associated with a comparatively higher likelihood of achieving CR and a lower hazard of death than blinatumomab.

In the absence of head-to-head trials, an indirect-treatment comparison can estimate the treatment effect of tisagenlecleucel in comparison with blinatumomab on rates of complete remission (CR) and overall survival (OS) in patients with relapsed or primary refractory (R/R) acute lymphoblastic leukemia (ALL). Patient-level data from two pivotal trials, ELIANA (tisagenlecleucel; n = 79) and MT103-205 (blinatumomab; n = 70), were used in comparisons of CR and OS, controlling for cross-trial difference in available patient characteristics. Five different adjustment approaches were implemented: stabilized inverse probability of treatment weight (sIPTW); trimmed sIPTW; stratification by propensity score quintiles; adjustment for prognostic factors; and adjustment for both prognostic factors and propensity score. Comparative analyses indicate that treatment with tisagenlecleucel was associated with a statistically significant higher likelihood of achieving CR and lower hazard of death than treatment with blinatumomab. The tisagenlecleucel group exhibited a higher likelihood of CR than the blinatumomab group in every analysis regardless of adjustment approach (odds ratios: 6.71-9.76). Tisagenlecleucel was also associated with a lower hazard of death than blinatumomab in every analysis, ranging from 68% to 74% lower hazard of death than with blinatumomab, determined using multiple adjustment approaches (hazard ratios: 0.26-0.32). These findings support the growing body of clinical trials and real-world evidence demonstrating that tisagenlecleucel is an important treatment option for children and young adults with R/R ALL.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy.[1,2] Approximately 20% of children and young adults with ALL will have primary refractory disease or relapse (R/R) during or after frontline therapy; for these patients, cure with chemotherapy alone is rare.[2,3] Rates of response decline with an increasing number of relapses, and R/R ALL remains a leading cause of cancer-related death in children and young adults despite currently available therapies.[4,5]

Immune therapeutic approaches to malignancy include aiming to overcome immune tolerance by modifying T-cell response via redirected T cells. Such approaches have the potential to provide clinical benefit

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Patient data analyzed in this paper were obtained from previously published data sets. For original data, please contact qiufei.ma@novartis.com.

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to patients with R/R ALL, including those who exhibit diminishing chemo-sensitivity and/or relatively chemo-resistant disease. CD19 is expressed on B cells and B-cell precursors, but not expressed on bone marrow stem cells, making CD19 an ideal target for treating B-cell ALL.[6]

Bispecific T-cell engagers (BiTE) employ a recombinant bispecific protein that simultaneously engages CD3 on T cells and an antigen on a malignant cell, thus mediating redirected T-cell activity toward the malignancy.[7] Blinatumomab, a CD3 × CD19-engaging synthetic small molecule, enables T cells ($CD3^+$) to recognize and eliminate CD19-positive B cells.[8] Blinatumomab received breakthrough therapy status in ALL and provides R/R ALL patients with a convenient and effective treatment approach that is distinct in its mechanism of action from historical salvage chemotherapy.[2]

Chimeric antigen receptor (CAR)-T cell (CAR-T) therapies are T cells that have been genetically engineered to express a synthetic CAR construct that reprograms lymphocyte specificity and function. While distinct from BiTE technology, mechanistically, both BiTE and CAR-T function to redirect T cells to target antigens that are expressed on malignancy; in this case, CD19. Tisagenlecleucel is a CD19-directed, genetically modified, autologous T-cell immunotherapy through which a patient's own T cells are reprogrammed with a transgene encoding an anti-CD19 CAR using the 4-1BB (CD137) co-stimulatory domain.[9] Use of the 4-1BB co-stimulatory domain augments T-cell antitumor activity and enhances CAR-T proliferation and persistence.[10] In contrast, current BiTEs do not provide costimulatory molecule engagement to the T cell, perhaps highlighting a key difference in the mechanism of action between these two immune-based therapies.

Blinatumomab and tisagenlecleucel are each indicated for the treatment of patients with R/R ALL. Comparing blinatumomab and tisagenlecleucel is challenging because the clinical trials evaluating these agents in children with ALL have been single-arm studies. Importantly, this type of study has provided the evidence upon which several approvals for ALL treatments were obtained.[11-14] Still, no head-to-head randomized trials of CD19-directed BiTEs and CAR-T exist. In this context, the most robust method to compare these two therapies is to perform an indirect comparison of their respective trials, adjusting for differences using patient-level data. Individual patient data enable statistical adjustment for differences in patient characteristics between patient populations with propensity score weighting,[15,16] facilitating more accurate and reliable comparisons instead of estimates provided by aggregate-level data.[16]

As no head-to-head trials have directly compared the efficacy of tisagenlecleucel with blinatumomab, the present study uses patient-level data obtained from existing publications[17-20] to control for available patient characteristics allowing us to estimate the impact of tisagenlecleucel on complete remission (CR) and overall survival (OS) with that of blinatumomab.

Materials and methods

ELIANA

ELIANA (NCT02435849) is a global, single-arm, multicenter phase 2 trial evaluating the efficacy and safety of tisagenlecleucel in heavily pretreated children and young adults (ages 3-21 years at diagnosis) with CD19+ R/R ALL.[18] Patients had to have ≥5% lymphoblasts in the bone marrow at screening, and could not have received prior anti-CD19 or gene therapy products.[18] The primary endpoint was best overall response (BOR) of either CR or complete remission with incomplete hematologic recovery (iCHR) within 3 months, assessed by an independent review committee on blood, bone marrow, cerebrospinal fluid, and physical examination. Responses had to be maintained for at least 28 days. OS was a secondary endpoint.[18] Most recent data are published in Maude et al (2018)[18] and Grupp et al (2018)[17]; this study is ongoing.

MT103-205

MT103-205 (NCT01471782) was an open-label phase 1/2 trial to determine the safety and efficacy of blinatumomab in pediatric (aged 2-17 years) patients with R/R B-cell precursor ALL. Patients had to have >25% bone marrow blasts and have ALL that was primary refractory, in first relapse after full salvage induction regimen, in second or later relapse, or in any relapse after allogeneic stem cell transplantation (alloSCT). ELIANA and MT103-205 both enrolled patients with primary refractory or second or later relapsed ALL and/or relapse after alloSCT.[17,20]

In study part 1, the primary endpoint was determination of the maximum tolerated dosage, which was a stepwise escalation in dosing from 5 $\mu g/m^2/d$ for the first 7 days to 15 $\mu g/m^2/d$ thereafter (5/15 $\mu g/m^2/d$).[19] In study part 2, the primary endpoint was the CR rate within the first two cycles. CR was defined as no evidence of circulating blasts or extramedullary disease and <5% blasts in bone marrow (M1). CR was subclassified on the basis of recovery of peripheral blood counts (full; incomplete; neither full nor incomplete). OS was a secondary endpoint. Primary efficacy and safety findings were published in von Stackelberg et al (2016),[19] and the final analysis including patient-level data was reported in Gore et al (2018).[20] The study was completed in May 2016, by which time all patients had either completed the 2-year follow-up, withdrawn from the study, or died.

The blinatumomab dataset published in Gore et al[20] was chosen as a comparator to the ELIANA tisagenlecleucel dataset because patient-level data on age, prior alloSCT, number of relapses, refractory disease status, and outcomes including survival and CR were available, as reported in Table 1 of the publication.[19] In addition, both were global pivotal trials with similar inclusion criteria.[17,20] The measurement time period of CR in ELIANA (best response of CR or iCHR within 3 months) is similar to that used in MT103-205 (best response of CR in first 2 cycles [12 weeks], including M1 marrow [full recovery of peripheral blood counts, incomplete recovery of peripheral blood counts, or neither full nor incomplete recovery]). Whereas ELIANA required maintenance of CR/iCHR response for at least 28 days, it is unclear whether MT103-205 had the same criteria.

Patient selection

All blinatumomab patients[20] received the recommended dose of 5/15 $\mu g/m^2/d$ and were eligible for and included in the current analysis. Any patient who received tisagenlecleucel infusion within ELIANA was included in the primary analysis and compared with blinatumomab. Not all patients enrolled in ELIANA received infusion due to disease progression or manufacturing reasons. To enhance rigor, all enrolled ELIANA patients, whether they received infusion or not, were included in the sensitivity analysis.

Table 1. Patient demographics

	Blinatumomab N = 70	Tisagenlecleucel infused N = 79	Tisagenlecleucel enrolled N = 97
Age (years), median (range)	8.0 (<1-17.0)	11.0 (3.0-24.0)	11.0 (3-27)
Male, n (%)*	47 (67.1)	45 (57.0)	54 (55.7)
Geographic region, n (%)*			
United States/Canada	22 (31.4)	44 (55.7)	56 (57.7)
European Union	48 (68.6)	28 (35.4)	32 (33.0)
Other	0 (0.0)	7 (8.9)	9 (9.3)
Karnofsky/Lansky performance status ≥50%, n (%)*	70 (100.0)	79 (100.0)	79 (81.4)
Previous alloSCT, n (%)	40 (57.1)	48 (60.8)	58 (59.7)
Previous relapses, n (%)			
0	2 (2.9)	6 (7.6)	8 (8.3)
1	31 (44.3)	21 (26.6)	29 (29.9)
2	29 (41.4)	17 (21.5)	18 (18.6)
≥3	8 (11.4)	35 (44.3)	42 (43.3)
Months since last relapse, median (range)*	2.9 (0.4-49.8)	3.5 (1.5-13.8)	NA
Bone marrow blast count ≥50%, n (%)*	52 (74.3)	54 (68.4)	70 (72.2)
Refractory to last treatment, n (%)	39 (56)	77 (53.8)	94 (55)

Variables describe patients at baseline of their respective trials.
At enrollment, blinatumomab patients had >25% bone marrow blasts; tisagenlecleucel patients had ≥5% lymphoblasts in bone marrow.
*Not considered in adjustment because of unavailability of patient-level data within the blinatumomab dataset published in Gore et al.[20]

Efficacy endpoints

The CR rate is a composite endpoint. The single term CR is used in this paper to avoid confusion; details of this composite endpoint are defined here and reiterated in other sections. The definition of CR is considered clinically similar between ELIANA and MT103-205, making the endpoints comparable in our analysis. In the tisagenlecleucel cohort, the CR rate was defined as the proportion of patients with best overall disease response of complete hematologic recovery or iCHR within 3 months. This was chosen because of post-CAR-T cytopenia, which is known to occur in some patients.[18] In the blinatumomab cohort, the CR rate was defined as the proportion of patients within two treatment cycles (12 weeks) with M1 marrow (no evidence of circulating blasts or extramedullary disease and <5% blasts in bone marrow) with either full recovery of peripheral blood counts, incomplete recovery of peripheral blood counts, or without full or incomplete recovery of peripheral blood count.

OS was defined as time from infusion of tisagenlecleucel to death (primary analysis) and time from enrollment to death (sensitivity analysis) in the tisagenlecleucel cohort. In the blinatumomab cohort, OS was defined as time from initiation of treatment to death.

Statistical assessments

The indirect comparison is based on published patient-level data, enabling inclusion of, and controlling for, baseline differences in patient characteristics between the two trials.[16] A variety of methods were used, including marginal and conditional models. A marginal model estimates average treatment effect for a population, whereas a conditional model estimates treatment effect among individuals with specific characteristics adjusting for differences in patient characteristics.

Complete response In the CR analysis, an odds ratio (OR) >1 indicates that tisagenlecleucel is associated with a higher odds of providing a response than blinatumomab. Statistical significance was considered at a level of 0.05 ($\alpha \leq 0.05$). The unadjusted OR was generated using univariate logistic regression; a multivariable logistic regression model adjusting for crosstrial differences in patient characteristics was used to produce an estimated conditional OR. In the adjusted CR analysis, using the same variables as previously described, multivariable logistic regression with adjustment by propensity score, prognostic factors, prognostic factors and propensity score, or (un)trimmed stabilized inverse probability of treatment weight (sIPTW) was performed. sIPTW was constructed using a propensity score model considering age, refractoriness to last treatment (yes/no), prior alloSCT, and number of prior relapses. A weighted logistic regression was then fitted with treatment as the only covariate. The upper and lower 1% of the sIPTW estimated above were trimmed. A weighted logistic regression based on the trimmed sIPTW was then fitted with treatment as the only covariate.

Overall survival analysis In the OS analysis, using blinatumomab as the reference arm, a hazard ratio (HR) <1 indicates that tisagenlecleucel is associated with a lower hazard of death than blinatumomab. Statistical significance was considered at a level of 0.05 ($\alpha \leq 0.05$). Kaplan-Meier curves were generated and compared using the log-rank test. The *P* values for OS comparisons at different months were obtained using the z-test. No adjustment for multiplicity was conducted. An HR was estimated using a univariate Cox model with treatment as the only covariate, which was the unadjusted analysis.

In the adjusted OS analysis, both marginal and conditional HRs between the two treatments were estimated after adjusting for differences in patient characteristics between the two populations.

The marginal HR was estimated via a weighted Cox regression model with treatment as the only covariate. The weights used were sIPTW, which was calculated based on the propensity score, estimated using a logistic regression model considering age, refractory to last treatment, prior alloSCT, and number of prior relapses. A trimmed weights approach was also used, where the upper and lower 1% of the sIPTW estimated were trimmed to avoid extreme weights to estimate marginal HR via a weighted Cox regression model. The conditional HR was estimated using Cox regression models with stratification by quantiles of propensity scores, or with adjustment by prognostic factors, or with adjustment for both prognostic factors and propensity scores.

Prognostic factors Prognostic factors were defined based on clinical relevance and the availability of the parameters in both datasets.

Prognostic factors were used to develop a propensity score to balance measured characteristics across patients treated with tisagenlecleucel compared with blinatumomab. Baseline patient factors that were adjusted for included age, treatment with prior alloSCT and number of prior relapses, and refractory to the last line of treatment, which are the patient-level data reported in MT103-205. In Table 1, baseline characteristics that were not considered prognostic factors because of unavailability of patient-level data within the blinatumomab dataset[20] are indicated with an asterisk.

The variable "treatment with prior alloSCT and number of prior relapses" had three levels: (1) with prior alloSCT; (2) no prior alloSCT with 0 or 1 relapse; and (3) no prior alloSCT with ≥2 relapses. Of note, because of inclusion criteria in MT103-205, the number of prior relapses was not reported for patients with prior alloSCT, as patients could enroll regardless of the number of prior relapses or refractory disease.[20]

Results

Patients

Seventy blinatumomab patients from MT103-205[20] and 79 patients from ELIANA (data cutoff date 1 July 2019) were included in the primary analysis. The sensitivity analysis included 70 blinatumomab patients and all 97 patients enrolled in ELIANA at data cutoff. Tisagenlecleucel data represent the primary infused cohort of 79 patients unless stated otherwise.

Demographics were generally similar between groups (Table 1); however, tisagenlecleucel-treated patients had more prior lines of therapy than those in the blinatumomab cohort. Specifically, there was a higher rate of patients with three or more prior lines of therapy in the tisagenlecleucel group. While the blinatumomab group had a higher blast cutoff for entry (25% vs 5%), the percentage of patients with a bone marrow blast count of >50% was relatively similar.

For OS comparisons, Cox proportional hazards assumptions were not violated in any unadjusted or adjusted analysis. Propensity score and inverse probability of treatment weight distributions were within the range of expected outcomes.

Complete remission rate

CR rates were higher with tisagenlecleucel (82%) than blinatumomab (39%). The tisagenlecleucel group exhibited a higher likelihood of CR than the blinatumomab group in both univariate (OR 8.09; 95% confidence interval [CI] 3.76-17.38; Table 2) and several multivariable analyses (OR adjusting for prognostic factors: 9.76; 95% CI 4.09-23.28; Table 2).

Overall survival

As shown in Figure 1, the OS with tisagenlecleucel was better than that with blinatumomab (median OS in months [95% CI]: not reached [not reached-not reached] vs 7.5 [4.2-12.4], log-rank $P <$ .01; Figure 1). Patients treated with tisagenlecleucel had higher OS rates at months 6, 12, and 18 than in those treated with blinatumomab (91% vs 54%; 82% vs 37%; 72% vs 26%, all $P <$ .001).

Tisagenlecleucel was associated with a lower hazard of death than blinatumomab in every analysis, ranging from 68% to 74% lower hazard of death than with blinatumomab, depending on adjustment approach (HR: 0.26-0.32; Table 3).

Sensitivity analysis

The tisagenlecleucel group exhibited a higher likelihood of CR than the blinatumomab group in both univariate (3.39; 95% CI 1.78-6.45; Table 4) and several multivariable analyses (HR adjusted for prognostic factors: 3.83; 95% CI 1.88-7.79; Table 4).

As shown in the Kaplan-Meier curves below, among all patients enrolled in ELIANA, OS with tisagenlecleucel was longer than that with blinatumomab (median OS in months [95% CI]: not reached [20.4-not reached] vs 7.5 [4.2-12.4], log-rank $P <$ .01; Figure 2).

Table 2. CR treatment effect of tisagenlecleucel vs blinatumomab

Method	OR	95% CI	*P*
Unadjusted OR			
Univariate logistic regression	8.09	3.76-17.38	<.0001
Marginal OR			
Logistic regression with sIPTW	7.80	3.66-16.60	<.0001
Logistic regression with trimmed sIPTW	7.49	3.52-15.96	<.0001
Conditional OR (adjusted)			
Logistic regression stratified by quintiles of propensity score	6.71	3.06-14.71	<.0001
Logistic regression adjusting for prognostic factors	9.76	4.09-23.28	<.0001
Logistic regression adjusting for prognostic factors and propensity score	9.71	4.03-23.40	<.0001

OR is the odds ratio of tisagenlecleucel vs blinatumomab. An OR >1 indicates that tisagenlecleucel is associated with a higher odds of response than blinatumomab.

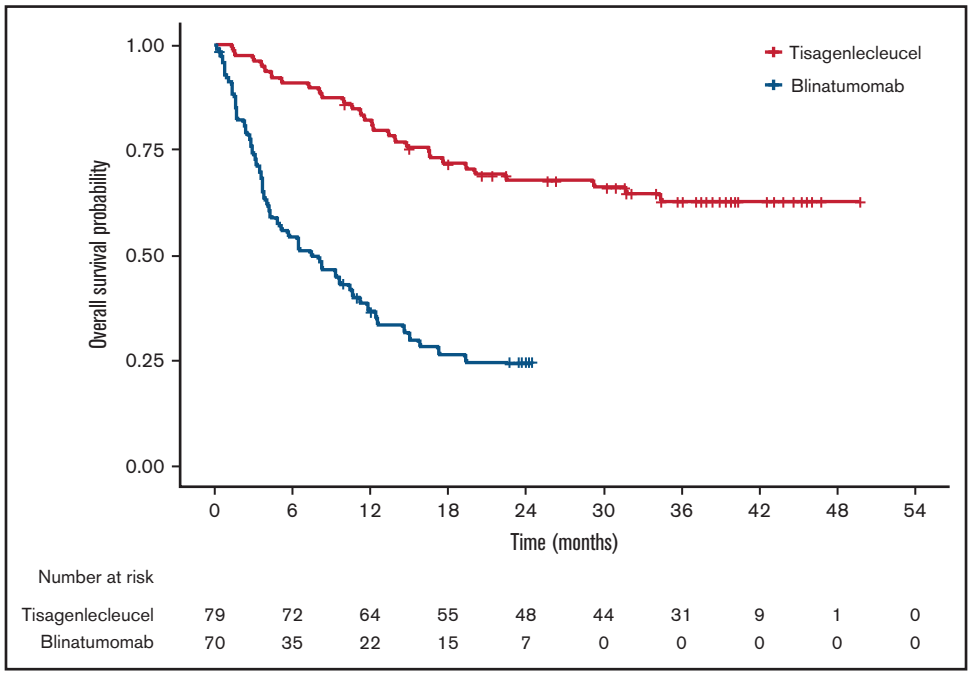

Figure 1. Observed OS from ELIANA (infused tisagenlecleucel) vs MT103-205 (blinatumomab).

Table 3. OS treatment effect of tisagenlecleucel versus blinatumomab

Method	HR	95% CI	*P*
Unadjusted HR			
Univariate Cox regression	0.26	0.16-0.43	<.001
Marginal HR (adjusted)			
Cox regression with sIPTW	0.31	0.19-0.50	<.001
Cox regression with trimmed sIPTW	0.31	0.19-0.50	<.001
Conditional HR (adjusted)			
Cox regression stratified by quintiles of propensity score	0.32	0.19-0.55	<.001
Cox regression adjusting for prognostic factors	0.26	0.16-0.45	<.001
Cox regression adjusting for prognostic factors and propensity score	0.26	0.15-0.44	<.001

An HR <1 indicates that tisagenlecleucel is associated with a lower hazard of death than blinatumomab after adjusting for prognostic factors.

Table 4. Sensitivity analysis: complete response treatment effect of tisagenlecleucel vs blinatumomab

Method	OR	95% CI	*P*
Unadjusted OR			
Univariate logistic regression	3.39	1.78-6.45	.0002
Marginal OR (adjusted)			
Logistic regression with sIPTW	3.46	1.82-6.59	.0002
Logistic regression with trimmed sIPTW	3.68	1.93-7.04	<.0001
Conditional OR (adjusted)			
Logistic regression stratified by quintiles of propensity score	3.08	1.56-6.09	.0012
Logistic regression adjusting for prognostic factors	3.83	1.88-7.79	.0002
Logistic regression adjusting for prognostic factors and propensity score	3.84	1.89-7.83	.0002

OR is the odds ratio of tisagenlecleucel vs blinatumomab. An OR >1 indicates that tisagenlecleucel is associated with a higher odds of response than blinatumomab.

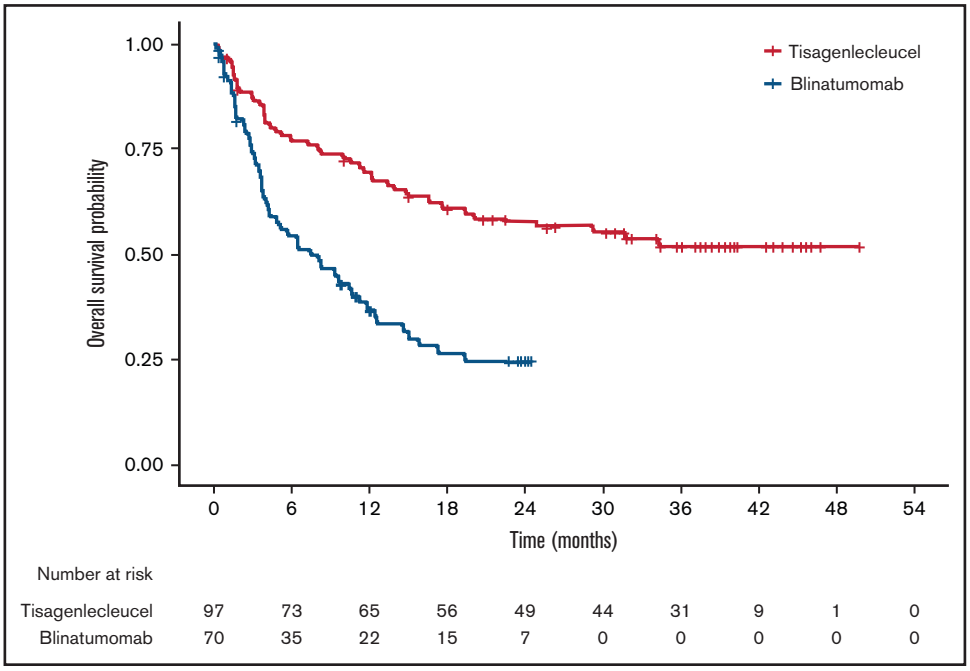

Figure 2. Sensitivity analysis: OS from ELIANA (enrolled tisagenlecleucel) vs MT103-205 (blinatumomab).

Patients treated with tisagenlecleucel had higher OS rates at months 6, 12, and 18 than those treated with blinatumomab (77% vs 54%, $P = .006$; 70% vs 37%, $P < .001$; 61% vs 26%, $P < .001$, respectively).

Tisagenlecleucel was associated with a 54% to 61% lower hazard of death than blinatumomab, depending on adjustment approach (HR: 0.39-0.46; Table 5).

Discussion

Although most children and young adults with ALL can be cured with frontline chemotherapy, refractory disease, or early and multiple relapses, are associated with poor treatment outcomes.[2] For those requiring additional lines of treatment, noncurative chemotherapies have historically been used to bridge the patient to allogeneic hematopoietic cell transplantation.[2] Among patients with R/R ALL, treatment can be intensive, protracted, and can last from months to years. During this time, patients and caregivers experience reduced quality of life and high levels of disease-, treatment-, and caregiver-related burden.[2,21,22] Here, we used published clinical trial data to compare the outcomes of patients treated with either blinatumomab or tisagenlecleucel, comparing both rates of remission and OS.

Blinatumomab was the first single-agent immunotherapy approved for R/R ALL and the first approved BiTE product. In the phase 1/2 MT103-205 study testing this agent in children, 39% of patients treated with the recommended dosage (5/15 μg/m^2/d) achieved a response (of whom 52% achieved minimal residual disease [MRD] negative response) with median survival of 7.5 months at 24 months.[19,20]

In the ELIANA trial, which tested tisagenlecleucel, a CD19-directed autologous CAR-T therapy, >80% of R/R ALL children and young adults achieved remission (of which 98% achieved MRD-negative bone marrow), and survival was durable (median duration not reached with median 24 months' follow-up).[17]

Table 5. Sensitivity analysis: overall survival treatment effect of tisagenlecleucel vs blinatumomab

Method	HR	95% CI	*P*
Unadjusted HR			
Univariate Cox regression	0.39	0.26-0.60	<.001
Marginal HR (adjusted)			
Cox regression with sIPTW	0.46	0.30-0.70	<.001
Cox regression with trimmed sIPTW	0.46	0.30-0.70	<.001
Conditional HR (adjusted)			
Cox regression stratified by quintiles of propensity score	0.46	0.29-0.71	<.001
Cox regression adjusting for prognostic factors	0.40	0.26-0.63	<.001
Cox regression adjusting for prognostic factors and propensity score	0.39	0.25-0.63	<.001

An HR <1 indicates that tisagenlecleucel is associated with a lower hazard of death than blinatumomab after adjusting for prognostic factors.

Both blinatumomab and tisagenlecleucel therapies gained initial US Food and Drug Administration (FDA) approval based on single-arm studies, and information directly comparing the two is difficult to obtain. In the absence of head-to-head trials, the present study used patient-level data from separate single-arm trials to compare the treatment effect of tisagenlecleucel and blinatumomab on CR and OS, accounting for the observed across-trial differences in patient characteristics.

Our study, the first patient-level indirect comparison study to evaluate blinatumomab vs tisagenlecleucel, found that tisagenlecleucel provides a significantly higher rate of CR and a significantly lower hazard of death than blinatumomab in both univariate and multiple multivariable analysis. The tisagenlecleucel group exhibited a substantially higher likelihood of CR than blinatumomab across multiple analyses. Whereas blinatumomab patients had a median survival of 7.5 months, by data cutoff in ELIANA, the median OS has not been reached with tisagenlecleucel at a median follow-up time of 38.8 months. The more favorable outcomes provided by tisagenlecleucel were consistent across multiple multivariable adjustment methods and were supported by sensitivity analysis findings. Our findings are also consistent with those of a previous matching-adjusted indirect comparison evaluating CR and OS between tisagenlecleucel and blinatumomab.[23]

Data from the real-world setting, such as that from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, which captures long-term data from recipients of CAR-T treatment and represents the largest set of safety and efficacy data for tisagenlecleucel, supports tisagenlecleucel response rates and safety findings observed in the clinical trial setting.[24] Indeed, CIBMTR registry reports determined a remission rate of 88% (n = 81/92) among patients infused with tisagenlecleucel. Most real-world evidence with blinatumomab is in adult populations and thus have not been reported here; however, the RIALTO expanded access study in pediatric patients reports median OS of 14.6 months from a median follow-up of 18.2 months,[25,26] and additional studies are ongoing.[27-29]

Compared with indirect analyses using aggregate data or using patient-level data for only one of the two interventions being compared, our analysis uses patient-level data from both ELIANA and MT103-205, enabling adjustment of patient characteristics in the current analysis. Firstly, not all prognostic variables are available for adjustment. Bone marrow blast count, remission duration, and Karnofsky/Lansky performance status were unavailable as patient-level data from MT103-205.[20] Therefore, they could not be used in the analyses. Secondly, despite our attempts to limit selection bias, there may be unobserved or unmeasurable differences between ELIANA and MT103-205 that could confound the comparison results. Lastly, safety outcomes are not compared as safety results are not reported at an individual level for blinatumomab.[20] Occurrence of extramedullary disease cannot be reported because data are not available with blinatumomab. The potential for treatment-emergent adverse events such as cytokine release syndrome (CRS) may be greater with tisagenlecleucel; however, in the postmarketing experience where infusion can be more easily timed, the rates of grade ≥3 CRS seem to be lower than those observed in the pivotal trial (16% vs 46%).[17,18,24] This paper compares survival outcomes with two different treatment strategies, with results reflecting the effect from study treatment as well as all subsequent treatments, including SCT. 36% (n = 25/70) and 20% (n = 16/79) of patients received subsequent allogeneic hematopoietic cell transplantation after blinatumomab and tisagenlecleucel, respectively. Of the 25 blinatumomab patients who received SCT, 10 were alive at the data cutoff date (survival time range: 23.5-24.3 months), two discontinued the study (survival time range: 10.9-12.0 months, censored at the time of discontinuation), three died with CR (survival time range: 3.1-14.6 months), six died with relapsed disease (survival time range: 3.2-19.4 months), and four were non-responders (survival time range: 2.7-15.8 months). Of the 16 tisagenlecleucel patients who received SCT, 13 were alive at the data cutoff date. Among alive patients, survival duration ranged from 11.5 months to 30.7 months. Survival time ranged between 11.6 and 16.6 months among the three patients who died prior to the most recent study assessment. While tempting to examine transplantation outcomes of these groups, the numbers are small, the types of therapies delivered in the event of blinatumomab or tisagenlecleucel failure and the MRD and remission status at the time of transplant are all unavailable and, thus, limit the interpretation of such data.

Bearing in mind these limitations, our analyses demonstrate a substantial magnitude of benefit with tisagenlecleucel compared with blinatumomab, as shown in OR and HR values, summarizing treatment effect on CR and OS, respectively. These findings are of note because evaluations of new treatments for pediatric R/R ALL populations most often demonstrate either no benefit or a moderate improvement in outcomes compared with standard treatment options.[30] In our study, consistency of the magnitude of benefit with tisagenlecleucel for both CR and OS was demonstrated across five different adjustment approaches in both the primary and sensitivity analyses (respectively, OR 6.71-9.76 and HR 0.26-0.32; OR 3.08-3.84 and HR 0.39-0.46). In addition, the size of the OR and HR values across multiple differing assessments decreases the likelihood of differences being substantially driven by potential confounding factors and suggests that results are describing a true treatment impact. We also note that limited advances to supportive care have been made during the time since the initiation of the Gore et al[20] trial and ELIANA trial (2012 and 2015, respectively) that may have benefited more recently enrolled tisagenlecleucel patients.

Blinatumomab and tisagenlecleucel are both immunotherapies, but considerable differences exist between their manufacturing requirements, ease of administration, and mechanisms of action, all of which might affect efficacy and usage. Blinatumomab is readily available as an off-the-shelf drug that requires continuous administration over the course of a month because of its high clearance rate and short half-life.[7,19,20,31] The ongoing infusion requirement of blinatumomab contrasts the personalized approach of tisagenlecleucel, which requires autologous T-cell collection, product shipping, in vitro culturing, and delivery to the treating center. However, the one-time infusion of tisagenlecleucel, which has the potential to persist long-term and may function similarly to immune memory cells by providing immunosurveillance against relapse, may counterbalance the initial wait for CAR-T production.[2,32] Similarly, whereas tisagenlecleucel is an individualized therapy modifying a patient's own T cells, the 'off-the-shelf' availability of blinatumomab enables a quick time to treatment of certain patient subgroups, such as those awaiting more definitive therapies.[33] Indeed, as a noncurative treatment option, we have previously shown that blinatumomab can be effective in a bridging capacity ahead of planned treatment with subsequent allogeneic hematopoietic cell transplantation.[33] Patients

typically proceed to subsequent allogeneic hematopoietic cell transplantation if they have achieved a treatment response and a donor is available. In ELIANA, approximately 20% of enrolled patients were not able to receive tisagenlecleucel for reasons including manufacturing issues (such as low initial slot availability in the clinical trial setting), death, or adverse event before infusion. In the real-world setting, these issues are not entirely mitigated but seem to be reduced with manufacturing process improvements.[24,34] Likewise, real-world data confirm high rates of tisagenlecleucel manufacturing success, as well as the possibility of delivering tisagenlecleucel in the outpatient setting, potentially minimizing health care resource utilization.[24] The decision to treat a patient with one therapy over another should be individualized and multifactorial, involving clinical, logistical, and patient preference considerations. Further investigation of tisagenlecleucel and blinatumomab in different clinical settings (eg, CASSIOPEIA, RIALTO) may offer additional insight with respect to patient selection.

Our study provides the first patient-level data indirect comparison of tisagenlecleucel versus blinatumomab in R/R ALL and confirms the substantial magnitude of benefit associated with tisagenlecleucel with respect to remission and survival. For the tisagenlecleucel population, we preferentially analyzed infused patients rather than all enrolled patients in the ELIANA trial so that our main findings are more informative for current practice; comparison of all enrolled patients is also provided as a sensitivity analysis. ELIANA was a pivotal and early clinical trial, run when tisagenlecleucel manufacturing capacity, process, and logistical management were less optimized than that currently achieved in clinical and commercial real-world environments. Evaluating the infused population as our primary analysis was decided in this context. Identification of true therapy effects is becoming more straightforward to assess as improved manufacturing enables faster turnaround times and higher proportions of eligible and/or intention-to-treat populations can receive the study drug.

There remains an ongoing unmet need to further understand clinical settings in which CAR-T therapy and blinatumomab provide the greatest benefit for patients. Consensus is lacking on when each treatment modality can be best used and remains an important clinical question. Comparative analyses indicate that treatment with tisagenlecleucel was associated with a statistically higher likelihood of achieving CR and a lower hazard of death than treatment with blinatumomab. The large differences in CR and OS outcomes across multiple differing assessments suggest that our findings describe a true treatment impact. Although the current analysis is retrospective and limited by cross-study comparison, these findings support the growing body of clinical trial and real-world evidence demonstrating that tisagenlecleucel is an important treatment option for children and young adults with R/R ALL.

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Authorship

Contributions: M.R.V., Q.M., J.Z., A.K., R.T., J.L., H.Y., A.A., and L.P. conceived of the project and designed the study, were responsible for the provision of study material or patients, collection and assembly of data, data analysis and interpretation, writing of the manuscript, and reviewed the data and contributed to critical revision of the manuscript.

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