Research Article

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Tisagenlecleucel versus historical standard therapies for pediatric relapsed/refractory acute lymphoblastic leukemia

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Aim: We compared outcomes from a single-arm study of tisagenlecleucel with standard of care (SOC) regimens in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia (ALL). **Methods:** The analysis included one tisagenlecleucel study, one blinatumomab study, one clofarabine monotherapy study, three studies of clofarabine combination regimens and two studies of other salvage chemotherapy. Matching-adjusted indirect comparison analyses were conducted. **Results:** After adjusting for baseline characteristics, tisagenlecleucel was associated with significantly prolonged overall survival compared with blinatumomab (hazard ratio [95% CI], 0.32 [0.16–0.64]); clofarabine monotherapy (0.24 [0.13–0.42]); clofarabine combination regimens (0.26 [0.15–0.45]); two salvage therapies (0.15 [0.09–0.25] and 0.27 [0.15–0.49]). **Conclusion:** The analysis demonstrated tisagenlecleucel was associated with substantially greater survival benefit versus all SOC regimens.

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Keywords: blinatumomab • CAR-T • clofarabine • pediatric and young adult acute lymphoblastic leukemia • salvage chemotherapy • tisagenlecleucel

Background

Pediatric acute lymphoblastic leukemia (ALL) is rare, with an annual incidence of approximately 3.4–4.0 cases per 100,000 children [1,2]. However, despite its rarity, ALL is the most common form of childhood cancer [1,2]. In the USA, there are over 3000 new cases of ALL diagnosed in children and adolescents each year [2].

Multi-agent chemotherapy forms the backbone of current ALL treatment. With such treatments, prognosis for ALL is good; however, 15–20% of children with ALL will eventually relapse [3]. Although 30–85% of children with relapsed ALL can achieve a second complete remission (CR) with intensive combination chemotherapy regimens and allogeneic hematopoietic stem cell transplantation (allo-SCT), most children will not survive despite these aggressive approaches [4–8]. Recent data from the Children's Oncology Group show that 5-year survival rates (± standard error) for relapsed/refractory (r/r) B-cell ALL, T-cell ALL and infant ALL were 52 ± 1%, 33 ± 3% and 19 ± 4%, respectively [9]. Based on data from one of the leading international pediatric study groups, Berlin-Frankfurt-Münster, four different risk groups can be identified (S1, S2, S3 and S4) according to the site of relapse, time from diagnosis to relapse and immune phenotype [3]. Among children in the S3 and S4 risk groups, relapsed ALL following chemotherapy and SCT is associated with extremely poor overall survival (OS), with a 5-year OS of <5% (following chemotherapy) and 30% (S3) and 25% (S4) with allo-SCT showing the importance of novel salvage treatments for this disease [3].

Several therapies have been approved for the treatment of pediatric and young adult patients with relapsed or refractory ALL since 2000. Clofarabine is a purine nucleoside metabolic inhibitor that induces programmed cell death by inhibiting DNA synthesis and DNA chain elongation/repair [10]. In 2003, clofarabine was approved in the US and European Union for treatment of pediatric and young adult patients with r/r ALL after ≥2 prior regimens [10,11]. Phase II study in children and young adults with r/r ALL treated with clofarabine monotherapy

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reported CR rate (CR or CRp: a CR with or without platelet recovery) of 20% and median OS of 13 weeks; the most common grade 3–5 adverse events (AEs) were febrile neutropenia (49%), anorexia (20%), hypotension (18%), nausea (16%) and pyrexia (15%) [12,13].

More recently, blinatumomab, designated by the US FDA as a breakthrough therapy, was approved for the treatment of r/r adult patients (18 years and older) with B-cell precursor ALL in 2014 and later on for pediatrics in 2016 [14,15]. Blinatumomab is a bispecific CD19-directed CD3 T-cell engager (BiTE) antibody, which activates previously unstimulated T cells and induces redirected lysis of CD19-positive cells [14,16]. In a pivotal Phashe I/II study (MT103-205) of blinatumomab in pediatric patients with r/r ALL, 39% of patients achieved CR within two treatment cycles (M1 [<5% blasts in bone marrow] with full recovery of peripheral blood counts = 17% [12/70]; M1 with incomplete recovery of peripheral blood counts = 16% [11/70]); M1 without full or incomplete recovery of peripheral blood counts = 6% [4/70]); the median OS was 7.5 months [17]. Among these patients, the most common grade 3–5 AEs were anemia (36%), thrombocytopenia (21%), febrile neutropenia (17%), hypokalemia (17%) and neutropenia (17%); 7% experienced fatal adverse events [17]. Same as clofarabine and other salvage chemotherapies, blinatumomab treatments are often used as 'bridges' to SCT in patients with relapsed disease [12,17,18].

Despite improvement in treatment, pediatric and young adult patients with r/r ALL still have a dismal prognosis and face imminent death: median OS with newly approved therapies is approximately 3–8 months [12,17], and the majority of children with r/r ALL still do not survive the disease. Maintaining a remission in previously relapsed patients is difficult, and the prognosis of patients with r/r disease remains poor. The 5-year overall survival in children receiving allo-SCT in $\geq$ third remission is ~30%. Only 17% of patients will receive a second SCT with a 3-year OS of 32% 5 year and 5-year OS of 22%. There remains an urgent unmet need for an effective treatment that offers improved survival independent of eligibility for SCT, delivers higher rates of hematologic CR rates and improves quality of life (QoL), with a lifetime benefit.

Tisagenlecleucel

Tisagenlecleucel is the first chimeric antigen receptor (CAR)-T cell therapy approved in the US, European Union, Canada, Switzerland, Australia and Japan for the treatment of patients up to 25 years old with r/r B-cell ALL [19–23]. In the pivotal, Phase II, single-cohort, 25-center global study, ELIANA (NCT02435849), a single infusion of tisagenlecleucel provided durable remission with long-term persistence of tisagenlecleucel and transient high-grade toxic effects in pediatric and young adult patients with r/r B-cell ALL. The CR rate (defined as proportion of patients with best overall disease response of CR or CRi (incomplete hematologic recovery) within 3 months was 82%, and all patients who had CR were found to be negative for minimal residual disease (MRD; MRD-negative defined as <0.01% as assessed by flow cytometry). The median duration of remission was not reached with median follow-up 9.1 months. Rates of OS were 90% (95% CI, 81%–95%) at 6 months and 66% (95% CI: 54%–76%) at 24 months [24]. In addition, clinically meaningful improvements in patient-reported QoL were observed as soon as 1–3 months after tisagenlecleucel infusion (beyond the period of acute toxicities) and persist for 12 months [25]. A total of 88% of patients had grade 3 or 4 AEs, mostly within 8 weeks after infusion ($\leq$8 weeks, 83%; >8 weeks to 1 year, 44%); 73% of patients had grade 3 or 4 AEs suspected to be related to tisagenlecleucel ($\leq$8 weeks, 69%; >8 weeks to 1 year, 17%). Select AEs within 8 weeks after infusion occurred in 89% of patients and included cytokine release syndrome (CRS; 77%), infections (43%), neurologic events (40%), cytopenias not resolved by day 28 (37%), febrile neutropenia (35%) and tumor lysis syndrome. Of note, major concern for AE is CRS, neurologic event and B-cell aplasia. All patients with a response to treatment had B-cell aplasia, and most patients in the study received immunoglobulin replacement in accordance with local practice [24]. There is no AE post-tisagenlecleucel infusion leading to study discontinuation.

Study objective

No randomized head-to-head trials have compared tisagenlecleucel with other salvage therapies (clofarabine, other chemotherapy regimens or blinatumomab). Absent head-to-head trials, matching-adjusted indirect comparison (MAIC) is a credible and widely used method for comparing treatment outcomes. MAIC analyses use individual patient data from trial(s) of one treatment to match the baseline summary statistics reported from trial(s) of a comparator [26]. After matching, treatment outcomes are compared across balanced trial populations using an approach similar to propensity score weighting [26]. It is one of the population-adjusted indirect comparison approaches recognized by the United Kingdom's National Institute for Health and Care Excellence and is well

accepted across various health technology assessment (HTA) bodies [27,28]. There are some known limitations to MAIC analyses that can result from unobserved cross-trial differences or the inability to match all outcome definitions or inclusion/exclusion criteria [26]. The objective of this study is to compare the treatment effects of tisagenlecleucel with standard of care (SOC) regimens using MAIC, adjusting for heterogeneity in baseline characteristics between study populations.

Methods

Systematic literature review

Database searches were performed in EMBASE, MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify records published in English from 1 January 2000 to 7 March 2018. In addition, gray literature sources were examined to identify any relevant abstracts from 2015 to 2018 meetings of the American Society of Clinical Oncology, European Cancer Organization/European Society for Medical Oncology, American Society of Hematology, European Hematology Association, American Society for Blood and Marrow Transplantation and European Society for Blood and Marrow Transplantation. Assessment and decision documents published by ten key HTA bodies were also reviewed to identify any clinical data used in submissions or assessments of interventions in the indication of interest that had not been published elsewhere. Clinical trial registries were also searched for relevant trials with available results. A supplemental search was conducted on adult evidence to ensure there were no data on subgroups of young adult patients ≤25 years of age. The screening for pediatric and adult searches were conducted separately, as the adult search covered articles published between 1 January 2000, and 1 April 2018.

Study eligibility criteria included randomized controlled trials, single-arm trials and observational studies that evaluated treatments of pediatric and young adult patients (aged ≤25 years) with r/r ALL and reported efficacy and safety outcomes. The SLR limited inclusion to any therapies that are licensed for any oncology indications. The only treatments that were not eligible were investigational therapies. Screening was conducted using a dual-screening approach, with two independent investigators reviewing each reference at the abstract and full-text levels. During both stages of screening, discrepancies between investigators were resolved through discussion, and a third investigator was involved if an agreement was not reached.

Relevance of the studies found was assessed based on treatment intervention (i.e., blinatumomab, clofarabine and salvage chemotherapy/treatment) and trial eligibility criteria. As this was a *post hoc* analysis of previously published data, no institutional board review was required.

Efficacy outcomes

Outcomes examined in the current analysis included OS and CR rate (defined as rate of CR, CRi, or CR with incomplete recovery of peripheral blood counts/platelet count). OS for tisagenlecleucel was defined as the duration from time of infusion to death due to any reason. The coordinates of published OS curves for the comparator treatments were extracted from the publications using the Engauge digitizer [29], and virtual event and censoring times were derived using the method published by Guyot *et al.* [30]. OS was compared using weighted Kaplan–Meier (KM) plots and weighted Cox regression. Other outcomes (e.g., relapse-free survival [RFS], event-free survival [EFS], duration of remission) were not included in this report because of the lack of reporting in most of the comparator studies.

Statistical analyses

MAICs were conducted for OS and CR rate. To ensure accurate comparisons, it is recommended to adjust for all prognostic variables and treatment effect modifiers [27]. The greatest possible set of adjustment variables includes all variables available both in the index trial data (i.e., tisagenlecleucel in this study) and reported in the published literature for the comparator study. However, each additional adjustment variable decreases the effect sample size and consequently the precision (not the accuracy) of the comparison [27]. Therefore, it is also recommended not to adjust for variables that are thought to be unrelated to outcomes. In these analyses, matching variable selection is a particular concern, as the sample sizes of the studies involved are relatively small.

Clinicians and the published literature were consulted to preselect the available matching variables before conducting the analyses. Recognizing that sample size loss is an inevitable consequence of adjustment and that priority should be given to adjusting the most important predictors of outcomes, we conducted two analyses for

each comparator: a base-case analysis where we adjusted for the most important variables, and a sensitivity analysis where we adjusted for additional variables.

The MAICs reweighted the tisagenlecleucel baseline characteristics to match the comparator baselines in all scenarios so that the weighted outcomes in ELIANA were statistically comparable to the observed outcomes in the comparator studies in the balanced trial populations. A nonanchor-based approach (i.e., comparing treatment arms without accounting for the common arm) was used in this analysis. OS curves were estimated by KM method. OS curves were compared using log-rank tests. Hazard ratios (HRs) were assessed using Cox proportional hazard models. CR rates were compared using chi-square tests by Wald test after matching and reported with 95% CI. Statistical significance was defined as p value less than 0.05.

Results

Systematic literature review

The database searches for the pediatric population yielded 2271 unique records for the pediatric population (Supplementary Figure 1). These records were screened based on titles and abstracts, after which 246 publications qualified for full-text review. During full-text screening, 177 records did not meet study selection criteria and were excluded, leaving 69 publications for inclusion from the pediatric database searches. In the supplemental adult searches, 2159 of a total 2730 records were screened at the title/abstract level, 182 met the criteria for full-text review and just one article included data on a subgroup of patients ≤25 years of age (Supplementary Figure 2). The study identified by the adult search included data for a subgroup of patients between 15 and 17 years of age, and no studies were identified with data on patients between 18 and 25 years of age. The gray literature search found additional publications that met the inclusion criteria, resulting in 83 total publications being included. Upon further review, it was determined that some publications reported on the same patient population, and 72 unique studies ultimately met the criteria for inclusion in the review. Following further assessment of the evidence, the included 72 studies were found to be heterogeneous regarding study design, patient characteristics (number of relapses, immunophenotypes and prior hematopoietic SCT), outcomes measured (OS, progression-free survival and relapse-free survival [RFS]) and treatment regimens examined.

Study selection

Of the three available studies on tisagenlecleucel in pediatric and young adult patients with r/r ALL, ENSIGN (NCT02228096) which was a US-only study [31], and study B2101J (NCT01626495) which was a single-center trial [32,33] were excluded. Therefore, the pivotal registrational, Phase II, single-arm, global ELIANA study (NCT02435849) was the only tisagenlecleucel study included in this analysis [34].

We identified ten studies of r/r ALL therapies with patient populations comparable to the ELIANA trial that could potentially be used as historical controls to compare treatment outcomes with tisagenlecleucel. Of these ten studies, two studies of clofarabine combination therapy (clofarabine + etoposide + cyclophosphamide [12]) were excluded because they did not report KM OS curves and OS could not be analyzed [35,36]. Because the RIALTO study, an expanded access study of blinatumomab [37], permitted enrollment of patients from the pivotal blinatumomab study (MT103-205) [17], it was excluded to avoid duplicate comparison. Therefore, the final MAIC included seven studies in addition to the ELIANA trial of tisagenlecleucel (Table 1).

Data sources

Individual patient data from ELIANA were used in the analysis. At time of data cutoff (13 April 2018), 79 pediatric and young adult patients with r/r B-cell ALL had been treated and the median duration of follow-up (from infusion to data cut-off) was 24.2 months [34]. Aggregated data for blinatumomab, clofarabine monotherapy, CEC, salvage polychemotherapy/high-dose single-agent regimens/stem-cell transplantation (salvage-1) and palliative therapy/salvage therapy ± second stem-cell transplantation (salvage-2) were extracted from the literature sources listed in Table 1.

Efficacy outcomes

Several studies reported overall remission or response rates, including the tisagenlecleucel [34], clofarabine monotherapy [12] and CEC combination studies [38–40], which were comparable to the definitions of CR rate used in the blinatumomab [17] and salvage-1 studies (Table 1) [4]. To avoid confusion, we refer to all of these as 'CR rates' throughout. The study of salvage-2 [41] did not report CR rates and therefore was not included in the comparison

Table 1. Characteristics of the studies included in the matching-adjusted indirect comparison analysis.

Study	Design	Treatment	Response criteria	N	Ref.
Maude *et al.* (ELIANA)	Pivotal, global, Phase II, single-cohort clinical trial	Tisagenlecleucel	Overall remission: best overall response of CR or CRi within 3 months by independent central review	79 (B-cell, 100%)	[34]
von Stackelberg *et al.* (MT103-205)	Pivotal, global, Phase I/II, single-arm clinical trial	Blinatumomab	CR within 3 months	70 (B-cell, 100%)	[17]
Jeha *et al.*	Phase II, single-arm, multicenter clinical trial	Clofarabine monotherapy	Overall remission: best response of CR or CRp by independent central review	61 (B-cell, 79%; T-cell, 8%)	[12]
Hijiya *et al.*	Phase II, single-arm, multicenter, clinical trial	CEC	Overall response: best response of CR or CRp after induction or reinduction by investigator review	25 (B-cell, 84%; T-cell, 4%)	[38]
Locatelli *et al.*	Phase II, single-arm, multicenter, clinical trial	CEC	Overall remission: CR or CRp	25 (B-cell, 68%; T-cell, 32%)	[39]
Miano *et al.*	Single-arm, multicenter, cohort study	CEC	Overall response: CR, CRp, or PR after first course and last course	24 (subtypes not reported)	[40]
von Stackelberg *et al.*	Retrospective cohort study from ALL-REZ BFM regimen study group	Salvage therapy (salvage-1), with three cohorts: • Curative: chemotherapy or SCT • Palliative: antineoplastic agents • Supportive: no antineoplastic therapy	Second CR at defined treatment time points according to relapse protocols	51 (B-cell, 11%; T-cell, 33%)	[4]
Kuhlen *et al.*	Retrospective analysis of BFM ALL-SCT-BFM 2003 and ALL-SCT-BFM international 2007 studies	Salvage chemotherapy after SCT failure with or without SCT vs palliative care (low-dose chemotherapy and/or supportive care only; salvage-2)	CR not reported	242 (B-cell, 73%; T-cell, 21%)	[41]

ALL-REZ BFM: ALL-relapse Berlin-Frankfurt-Münster; BFM: Berlin-Frankfurt-Münster; CEC: Clofarabine plus etoposide plus cyclophosphamide combination therapy; CR: Complete remission; CRi: CR with incomplete hematologic recovery; CRp: CR without platelet recovery; SCT: Stem cell transplantation.

of CR rates. RFS (not censored at hematopoietic SCT) was only reported in the blinatumomab study; EFS was only reported in salvage-1 and salvage-2.

Table 2 lists the available variables considered for all the comparisons. For ELIANA, median number of previous line of therapies is 3 with range 1–8. Blinatumomab MT103-205 trial does not provide line of therapy data. However, number of previous relapses was provided (median: 2). Therefore number of previous relapses variable was used in matching between tisagenlecleucel and blinatumomab. The MAICs successfully reweighted the tisagenlecleucel baseline characteristics to match the comparator baselines, as shown in Table 3.

After matching for baseline clinical characteristics, tisagenlecleucel was associated with significantly prolonged OS compared with blinatumomab (HR: 0.32 [95% CI: 0.16–0.64]; $p = 0.0015$), clofarabine monotherapy (0.24 [0.13–0.42]; $p < 0.0001$), CEC (0.26 [0.15–0.45]; $p < 0.0001$), salvage polychemotherapy/high-dose single-agent regimens/stem cell transplantation (salvage-1; 0.15 [0.09–0.25]; $p < 0.0001$) and palliative therapy/salvage therapy ± second stem cell transplantation (salvage-2; 0.27 [0.15–0.49]; $p < 0.0001$; Table 4). OS KM curves for the base-case MAICs are presented in Figure 1. OS KM curves from the sensitivity analyses were similar. Matched tisagenlecleucel KM curves differed from the unmatched tisagenlecleucel KM curves by a small fraction of the difference between the tisagenlecleucel and comparator curves.

CR rate comparisons were made against all comparator treatments, except salvage-2, as the study did not report CR rate data [41]. Of note, definition of CR in tisagenlecleucel ELIANA trial (best response of CR or CRi) is comparable to that in blinatumomab (full recovery of peripheral blood counts, or incomplete recovery of peripheral blood counts or neither full nor incomplete recovery) and clofarabine trials (CR or CRp, with or without platelet recovery). As shown in Table 5, tisagenlecleucel was associated with significantly higher CR rates compared with all other treatments, with odds ratios ranging from 4.1 (versus CEC) to 12.9 (versus clofarabine monotherapy). The adjusted tisagenlecleucel response rates ranged from 76 to 83%, a substantial improvement over the comparator treatments. CR rates were 39% with blinatumomab, 49% with CEC, 20% with clofarabine monotherapy and 31% with salvage-1. The magnitudes of improvement in OS and CR rates were generally consistent between the base-case and sensitivity analyses.

Table 2. Baseline characteristics for matching-adjusted indirect comparison consideration.

Comparison	Variables
Tisagenlecleucel vs blinatumomab	Median age, years
	Sex, %
	Geographic region, %
	Previous relapses, %
	Months since last relapse
	Blast count†, %
	CNS involvement, %
	Testicular involvement, %
	Prior HSCT, %
Tisagenlecleucel vs clofarabine monotherapy‡	Age, years
	Sex, %
	Race and ethnicity, %
	Prior lines of therapy, %
	Prior HSCT, %
Tisagenlecleucel vs CEC (pooled)	Sex, %
	Prior HSCT, %
Tisagenlecleucel vs salvage-1§	Age, years
	Sex, %
	Prior lines of therapy, %
Tisagenlecleucel vs salvage-2¶	Sex, %
	Previous relapses, %
	Months from most recent SCT to relapse

†Measured at enrollment for tisagenlecleucel.
‡Polychemotherapy/high-dose single-agent regimens/stem-cell transplantation.
§To preserve sample size, only tisagenlecleucel patients with one prior line were excluded.
¶Palliative therapy/salvage therapy ± second stem-cell transplantation.
CEC: Clofarabine plus etoposide plus cyclophosphamide combination therapy; CNS: Central nervous system; HSCT: Hematopoietic stem cell transplantation; SA: Sensitivity analysis; SCT: Stem cell transplantation.

Discussion

Results of the global, pivotal Phase II ELIANA study of tisagenlecleucel in pediatric and young adult r/r B-cell ALL showed that tisagenlecleucel provided durable clinical remission and prolonged survival with a manageable safety profile [24]. However, absent head-to-head randomized trials, the magnitude of benefit over SOC regimens is unknown. We conducted a systematic literature review to identify the most relevant comparator treatments for tisagenlecleucel in this patient population, followed by MAIC to indirectly compare outcomes between regimens. All adjustment scenarios showed that tisagenlecleucel was associated with large benefit for pediatric and young adult patients with r/r ALL versus blinatumomab, CEC combination therapy, clofarabine monotherapy, salvage-1 and salvage-2 with regard to OS and CR rates. After adjustment, patients who received tisagenlecleucel were significantly more likely to experience CR and were estimated to be more than twice as likely to survive the first year.

Like other MAIC analyses, these analyses are limited by various assumptions inherent to the methodology. The MAIC analysis was conducted under the assumption that adjusting for patient baseline characteristics was sufficient to explain all differences in trial outcomes, that all important patient characteristics were reported and adjusted for, and that there were no subgroup effects or treatment effect modifiers. Any structural differences between studies remain unadjusted for. Second, eighteen (18.6%) out of 97 patients enrolled in ELIANA trial were not able to receive tisagenlecleucel, due to manufacture issue, dealth or adverse event before infusion. The added benefit using OS from enrollment (intent to treat [ITT] analysis) will be less, comparing tisagenlecleucel versus historical data. However, with improvement in manufacture process and expansion of global manufacture footprint overtime, the number of patients not able to receive tisagenlecleucel will continue to decrease in the real world. The ITT analysis based on trial data will likely underestimate the benefit of tisagenleceleucel in the real-world setting. Third, it was not possible to adjust for patients with T-cell ALL in the comparisons of tisagenlecleucel with CEC and salvage-1 because ELIANA did not include patients with T-cell ALL; the percentage of patients with T-cell ALL was 32% in one of the CEC trials and was 33% in the salvage-1 trial. The percentage of patients with T-cell ALL

Table 3. Baseline characteristics before and after matching.

Comparison		Tisagenlecleucel unmatched	Tisagenlecleucel matched	Comparator
Tisagenlecleucel vs blinatumomab				
Previous relapses, %	0	7.6	2.9	2.9
	1	17.7	44.3	44.3
	2	26.6	41.4	41.4
	≥3	48.1	11.4	11.4
Prior HSCT, %		60.8	57.1	57.1
Tisagenlecleucel vs clofarabine monotherapy				
Prior lines of therapy, %	1	5.1	0	0
	2	27.8	37.7	37.7
	3	25.3	36.1	36.1
	4	19.0	21.3	21.3
	≥5	22.8	4.9	4.9
Prior HSCT, %		60.8	29.5	29.5
Tisagenlecleucel vs CEC (pooled)				
Prior HSCT, %		60.8	27.0	27.0
Tisagenlecleucel vs salvage-1[†]		NA	NA	NA
Tisagenlecleucel vs salvage-2[‡]				
Months from most recent SCT to relapse, %	≤6	45.8	40.9	40.9
	6–12	10.4	27.7	27.7
	>12	43.8	31.4	31.4

[†]Polychemotherapy/high-dose single-agent regimens/stem cell transplantation. Note that those who had 1 prior therapy was excluded from ELIANA before matching. No matching variable was used in this comparison due to matching failure of number of prior line of therapy.
[‡]Palliative therapy/salvage therapy ± second stem cell transplantation.
CEC: Clofarabine plus etoposide plus cyclophosphamide combination therapy; HSCT: Hematopoietic stem cell transplantation; SCT: Stem cell transplantation.

Table 4. Overall survival before and after matching.

Adjustment scenario	Observed median OS, months	Before matching		After matching	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Tisagenlecleucel vs blinatumomab	NR (in 35 mo) vs 7.5 mo	0.28 (0.17–0.46)	<0.0001	0.32 (0.16–0.64)	0.0015
Tisagenlecleucel vs clofarabine monotherapy	NR (in 35 mo) vs 3.3 mo	0.17 (0.10–0.28)	<0.0001	0.24 (0.13–0.42)	<0.0001
Tisagenlecleucel vs CEC (pooled)	NR (in 35 mo) vs 4.6 mo	0.22 (0.13–0.36)	<0.0001	0.26 (0.15–0.45)	<0.0001
Tisagenlecleucel vs salvage-1[†]	NR (in 35 mo) vs 4.0 mo	0.14 (0.08–0.23)	<0.0001	0.15 (0.09–0.25)	<0.0001
Tisagenlecleucel vs salvage-2[‡]	NR (in 35 mo) vs 6.0 mo	0.28 (0.19–0.43)	<0.0001	0.27 (0.15–0.49)	<0.0001

[†]Polychemotherapy/high-dose single-agent regimens/stem-cell transplantation.
[‡]Palliative therapy/salvage therapy ± second stem-cell transplantation.
CEC: Clofarabine plus etoposide plus cyclophosphamide combination therapy; HR: Hazard ratio; NR: Not reached; OS: Overall survival.

Table 5. Comparison of CR rates before and after matching.

Adjustment scenario	Observed CR rate, %	Before matching		After matching	
		Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Tisagenlecleucel vs blinatumomab	82 vs 39	7.39 (3.49–15.68)	<0.0001	7.77 (2.62–23.01)	0.0002
Tisagenlecleucel vs clofarabine monotherapy	82 vs 20	18.96 (8.06–44.60)	<0.0001	12.88 (5.02–33.04)	<0.0001
Tisagenlecleucel vs CEC (pooled)	82 vs 49	4.90 (2.35–10.23)	<0.0001	4.11 (1.84–9.21)	0.0006
Tisagenlecleucel vs salvage-1[†]	82 vs 31	10.16 (4.44–23.21)	<0.0001	9.53 (4.16–21.84)	<0.0001
Tisagenlecleucel vs salvage-2[‡,§]	82 vs NA	NA	NA	NA	NA

[†]Polychemotherapy/high-dose single-agent regimens/stem cell transplantation.
[‡]Palliative therapy/salvage therapy ± second stem cell transplantation.
[§]The salvage treatment study did not report CR rates.
CEC: Clofarabine plus etoposide plus cyclophosphamide combination therapy; CR: Complete remission; NA: Not available.

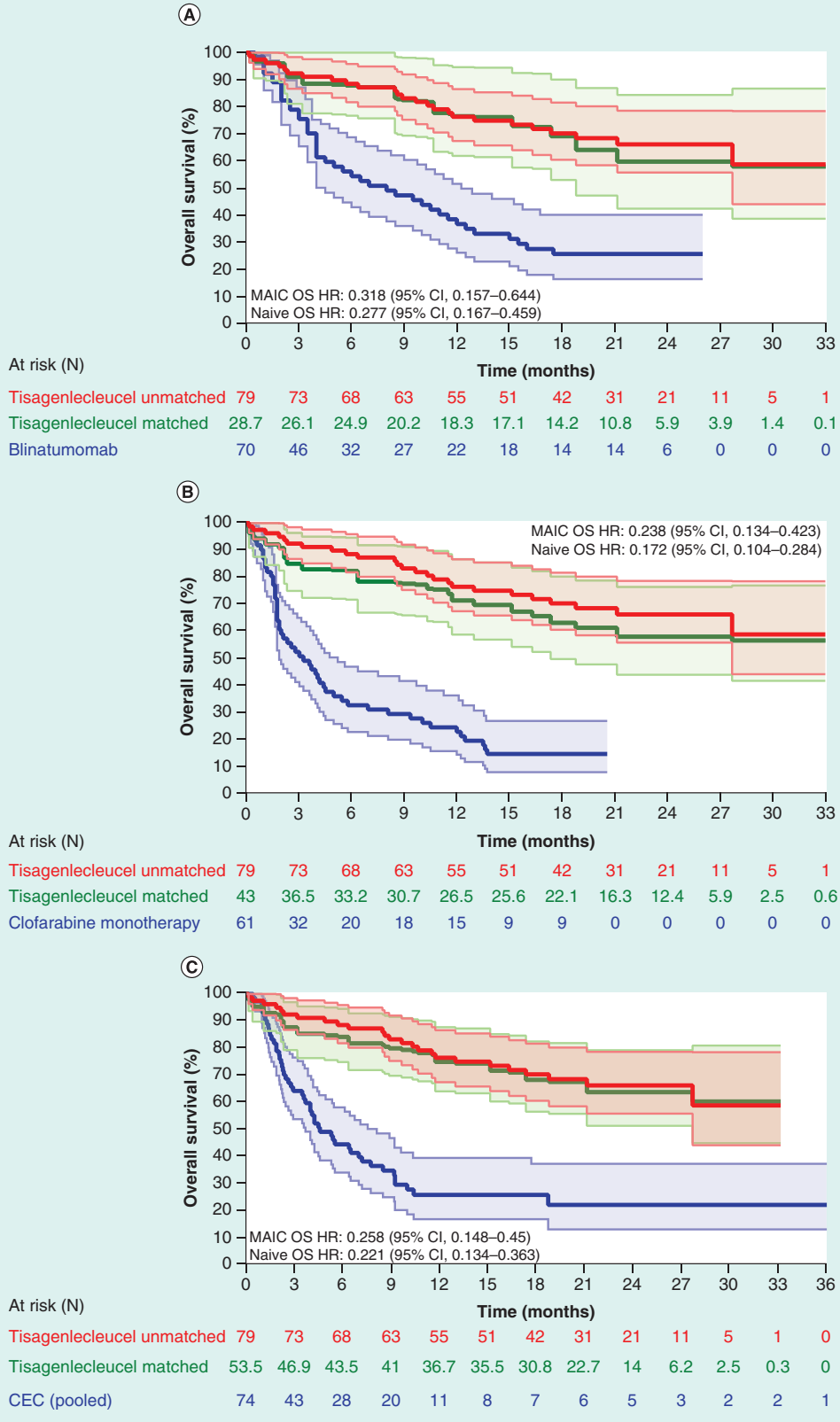

Figure 1. Comparison of OS before and after matching, with 95% CIs: Tisagenlecleucel against (A) blinatumomab, (B) clofarabine monotherapy, (C) CEC, (D) salvage-1 and (E) salvage-2.

A mix of therapies that were classified as palliative and salvage chemotherapy with and without second stem cell transplantation.

CEC: Clofarabine plus etoposide plus cyclophosphamide combination therapy; HR: Hazard ratio; KM: Kaplan–Meier; MAIC: Matching-adjusted indirect comparison; OS: Overall survival.

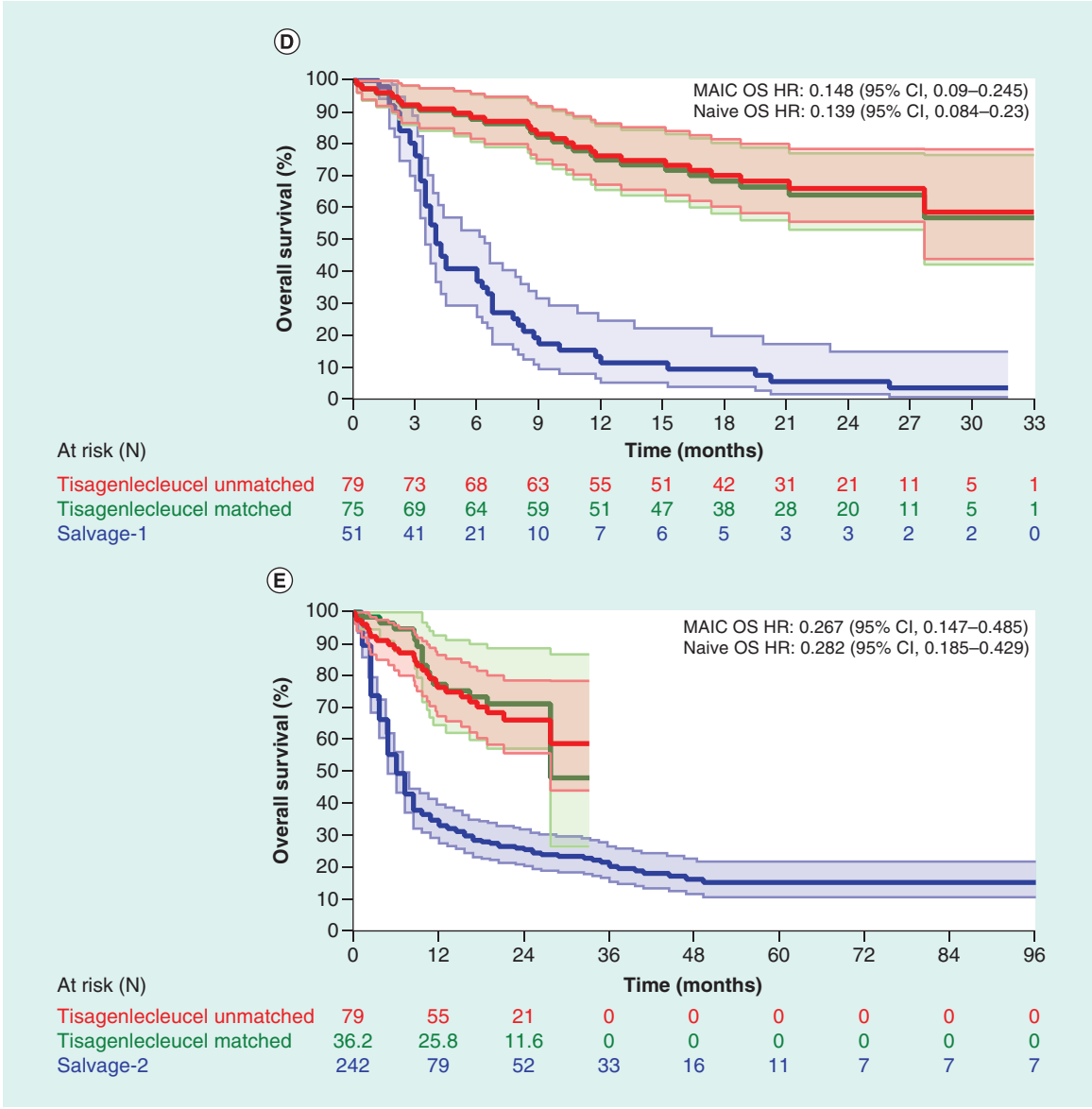

Figure 1. Comparison of OS before and after matching, with 95% CIs: Tisagenlecleucel against (A) blinatumomab, (B) clofarabine monotherapy, (C) CEC, (D) salvage-1 and (E) salvage-2 (cont.).
A mix of therapies that were classified as palliative and salvage chemotherapy with and without second stem cell transplantation.
CEC: Clofarabine plus etoposide plus cyclophosphamide combination therapy; HR: Hazard ratio; KM: Kaplan–Meier; MAIC: Matching-adjusted indirect comparison; OS: Overall survival.

in the other studies were ≤21%. The comparison result with CEC and salvage therapy should be interpreted with caution. Furthermore, due to the lack of reference arms in the studies involved, it was not possible to conduct anchored comparisons or test for residual confounders. Last, literature review end date is March 2018. Any relevant comparator with publication since 2018 would not be included in this analysis.

Despite these limitations, given the magnitude of the clinically meaningful differences observed, these analyses likely are the best available evidence on the comparative efficacy of treatments in r/r pediatric and young adult patients with ALL. All studies used in this analysis, and almost all studies identified in the systematic literature review, are single arm. Consequently, a network meta-analysis approach is not possible, and statistical techniques such as MAIC are the most robust method for estimating relative efficacy. Obtaining reliable estimates of relative efficacy is a crucial step in supporting comparative research and health economic evaluations. To our knowledge,

this is the first analysis built upon systematic literature review that estimates the relative efficacy of treatments in pediatric and young adult patients with r/r ALL in the post-CAR-T approval time period.

In summary, this study shows that tisagenlecleucel is associated with substantial clinical benefit over SOC regimens for pediatric and young adult patients with r/r ALL. Given the magnitude of disparities among treatment outcomes, it is highly unlikely that any residual confounders are responsible for the differences in efficacy.

Conclusion

This analysis used MAIC methodology to indirectly compare efficacy outcomes between tisagenlecleucel and SOC regimens, including blinatumomab, clofarabine monotherapy, CEC and salvage chemotherapy/treatment, as treatment for pediatric and young adult patients with r/r ALL. After adjusting for cross-study differences, tisagenlecleucel was associated with significantly longer OS and significantly higher CR rates compared with SOC regimens, with substantial magnitudes of improvement before and after MAIC. Real-world registry studies are warranted to confirm the magnitude of tisagenlecleucel benefit versus other treatments.

Summary points

- Tisagenlecleucel is an anti-CD19 chimeric antigen receptor therapy that induced complete remission in 82% of children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia treated in the ELIANA trial, and had a manageable safety profile.
- Before our study, there was a paucity of information about comparative effectiveness in patients treated with chimeric antigen receptor therapy versus historical standard of care (SOC).
- A systematic literature review was taken and eight single-arm trials were identified including blinatumomab, clofarabine monotherapy, clofarabine combination therapy and salvage chemotherapy. In this study, we applied matching-adjusted indirect comparison to evaluate the clinical efficacy of tisagenlecleucel against historical data.
- The analysis demonstrated tisagenlecleucel was associated with substantially greater survival benefit versus all historical SOC regimens.
- To our knowledge, these results represent the first report of comparative effectiveness of a novel CAR-T treatment versus historical SOC regimens in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia.

Author contributions

All authors were involved in the conception and design, or analysis and interpretation of the data; Q Ma was involved in the drafting of the paper; all authors were involved in revising the manuscript critically for intellectual content and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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