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Allogeneic hematopoietic stem cell transplantation after CD19-directed CAR T-cell therapy in children and adults with B-cell acute lymphoblastic leukemia: a GoCART coalition study on behalf of the PDWP, ALWP, and CTIWP of the EBMT

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Allogeneic hematopoietic stem cell transplantation after CD19-directed CAR T-cell therapy in children and adults with B-cell acute lymphoblastic leukemia: a GoCART coalition study on behalf of the PDWP, ALWP, and CTIWP of the EBMT

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Running Title: Consolidative, pre-emptive or rescue transplantation after CAR-T cell therapy in B-ALL

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Abstract

Hematopoietic stem cell transplantation (HSCT) can rescue B-cell acute lymphoblastic leukemia (B-ALL) recurring after CD19-directed chimeric antigen receptor T cells (CAR19 T cells). However, in patients at high risk of relapse, the indication for and timing of consolidative HSCT are controversial. We retrieved data on 112 patients who received an HSCT at a median of 6.1 months after CAR19 T-cell infusion. Indication for subsequent HSCT were: (I) Rescue in 72 (64%) patients for disease recurrence; (II) Pre-emptive in 21 (19%) for loss of B-cell aplasia; (III) Consolidative in 19 patients (17%). The 2-year post-transplant Leukemia-Free Survival (LFS) was 54% and the 2-year cumulative incidence of relapse was 32%. Children had better LFS than adults (63% vs 38%). Older age was associated with inferior LFS (HR per 10-year increase 1.30; p= 0.01) and patients receiving a rescue HSCT had a significantly lower 2-year LFS (41%), compared to pre-emptive (74%) and consolidative HSCT (78%), respectively (p=0.002). Haploidentical donor was also associated with inferior LFS (HR: 2.21 95%CI: 1.15-4.25, p=0.02). This "real-world" study corroborates the need to identify patients at higher risk of relapse and optimization of strategies to improve outcome in patients with R/R B-ALL receiving CD19-directed CAR T cells.

Introduction

CD19-directed chimeric antigen receptor T cells (CAR19 T cells) represent a major breakthrough in the treatment of relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) in children and adults. However, many patients receiving CAR19 T cells require further anti-leukemic intervention either to treat emergent minimal residual disease (MRD) or to consolidate remission[1]. In the pivotal ELIANA trial 22% of patients underwent consolidation with haematopoietic stem cell transplantation (HSCT) and, more recently, data on larger sets of patients treated with tisagenlecleucel in a real-world setting showed that around 25% of patients (children and adults) receive HSCT[2].

Taken together, these data suggest that approximately 40-50% of patients have presented signs of disease recurrence (overt morphological relapse or MRD positivity), and, despite several collaborative efforts, identification of patients at higher risk of CAR-T treatment failure remains challenging[3-6]. Long-term disease remission is usually associated with persistence of CAR-T cells, which should prevent CD19-positive disease relapse[3,5,7]. On the other hand, a subgroup of patients experience CD19-negative relapse in the presence of circulating CAR T cells, possibly due to immune escape (CD19 loss/masking, expansion of CD19-negative clones) or lineage switch[3,8,9]. Therefore, it remains debated for which patients CAR19 T-cell therapy can be considered a stand-alone treatment, and which patients may benefit from consolidation of remission with HSCT. According to expert consensus and current practice, several factors might prompt consideration of HSCT, including early loss of CAR-T cells, low peak of expansion after infusion, high disease burden prior to CAR-T, presence of *KMT2A*-rearrangements, besides the CAR-T construct (e.g. 4-1BB vs CD28 co-stimulatory domain)[10–12]. However, to date, data on the impact of HSCT after CAR-T are lacking and mainly related to small groups of patients, with no stratification according to post-CAR-T disease status. Some investigators consider consolidative HSCT as standard of care when disease remission is achieved after CAR-T, while others wait for

signs of CAR-T failure before any intervention. Whether early HSCT might provide a survival benefit is unknown, especially for patients who already received HSCT before CAR-T. Furthermore, no clear data are available on the role of donor source or intensity of conditioning on the success of transplant procedures after CAR-T cell therapy.

In this GoCART Coalition/EBMT study we investigated the outcome of HSCT following CAR19 T-cell therapy in children and adults with B-ALL, and the impact of specific patient-, disease-, and transplant-related factors on outcomes.

Methods

Study design and data collection

This study was supported by the GoCART Coalition, a consortium created by the European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT). Retrospective data were retrieved from the EBMT registry on adults and children with B-ALL who received autologous CAR19 between 2016 and 2023. Patients receiving allogeneic CAR19 T-cell product were excluded. Baseline, previous treatment, bridging therapy, CAR19 T-cell product, B-cell aplasia duration, outcome, disease status at follow-up were collected. All centers reporting patients were contacted to contribute and provide additional treatment and follow- up information using data documentation fields. Quality control and query resolution were conducted by the EBMT Study Unit. Participating centers had obtained written informed consent for registration within EBMT, according to the Declaration of Helsinki. The study (code: 8426002) was selected and approved by the GoCART coalition.

Patient characteristics and HSCT procedures

Data on post-CAR -T HSCT conditioning regimen, donor and stem cell source were collected; information regarding indication to HSCT was requested from participating centers. Myeloablative regimens (MAC) included the use of 12Gy total body irradiation (TBI), busulfan

or treosulfan, while any other regimen was considered as reduced intensity (RIC)[13]. We described patients according to CAR-T persistence and disease status at the time of transplant: HSCT was labelled as (I) *Rescue HSCT* when performed in patients after experiencing MRD positivity (as defined by the participating center) or overt disease relapse post CAR19 T cell therapy; (II) *Pre-emptive HSCT* when performed in patients due to loss of B-cell aplasia and/or loss of detectable CAR-T with no signs of disease recurrence; (III) *Consolidative HSCT* when performed in patients who had ongoing B-cell aplasia and no evidence of disease recurrence.

Presence of CD19-negative clones were reported at any time-point when investigated (e.g. before CAR19 T cells, post- CAR19 T cells, post-HSCT).

Complete remission was defined as <=5% blasts in a regenerating bone marrow and no signs of extramedullary disease (EMD), while MRD negativity was defined according to each participating center, whichever method was used. Cytogenetic/genomic risk was classified based on 2024 ELN criteria[14].

Endpoints, definitions and statistical analysis

The primary objective was to evaluate factors associated with leukemia-free survival (LFS) after allo-HSCT. LFS was defined as absence of disease, being MRD negative and alive from HSCT to last follow-up. Secondary outcomes were overall survival (OS), relapse incidence (RI), non-relapse mortality (NRM), acute GVHD grade II-IV and III-IV, chronic GVHD and GRFS (Graft-versus-Host Disease-Free, Relapse-Free Survival). Relapse was defined as molecular or hematologic recurrence (including in extra-medullary sites) of the disease. B cell aplasia and CAR-T cells persistence was defined according to local practice. GvHD, molecular/overt Relapse Free Survival was defined as first event of acute GVHD grade II-IV, moderate, severe or extensive chronic GVHD, relapse or death. All the outcomes were calculated from the date of HSCT post CAR19 T cell therapy. Kaplan-Meier estimates were used to estimate OS and LFS

and GRFS, whereas cumulative incidence was used for relapse incidence (RI), non-relapse mortality (NRM) and GVHD outcomes. Relapse and NRM were mutually competing events. Death was a competing event for GVHD outcomes. Surviving patients were censored at the time of last follow-up. Survival probabilities and cumulative incidence results were calculated as estimates and 95% confidence intervals. Multivariable analyses for OS, LFS, RI, NRM and GRFS were performed using the Cox proportional hazards regression model. Included variables were reasons for HSCT, age at HSCT, donor type, disease status and use of TBI. Due to the number of events and patients, only variables with most clinical known impact were included in the models. The median follow-up was calculated using Reverse Kaplan-Meier method. Statistical test values were two-sided, with statistical significance evaluated at the 0.05 alpha level. All analyses were performed using R version 4.5.2 (R Core Team (2025). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org).

Results

Patients baseline features and disease characteristics

Of 344 patients (172 adults and 172 children) infused with CAR19 T cells, 112 subsequently received an HSCT, corresponding to a 2-year cumulative incidence of HSCT after CAR19 of 34% (95% CI 28.8–39.5). Patients' characteristics are summarized in **Table I** and **Table S1.** Patients from 24 centers received HSCT at a median age of 13.9 years (range 1.5-67.8) with a median post-transplant follow-up of 2.1 years (95%CI 1.9-2.5). Overall, 66/112 (59%) patients were transplant-naive, and 2 patients already received two HSCT before CAR19 T cells infusion. For patients that had been transplant-exposed, previous relapse had occurred mainly > 6 months after the first transplant (80%) and the median time between the pre-CAR transplant procedure and the post-CAR HSCT was 2.5 years (IQR 1.8-3.7).

Regarding previous immunotherapy, only a minority of patients had received blinatumomab (20%, 22/111) or inotuzumab ozogamicin (18%, 20/111) before CAR19 T cells therapy, and, overall, 67% (74/111) of patients received no immunotherapy (one patient missing). Among patients that received blinatumomab or inotuzumab ozogamicin before CAR19 T cells therapy, 10/22 (46%) and 7/20 (35%) patients did not respond to the immunotherapy, respectively. Only a minority of patients presented with *KMT2A*-rearrangement (10%, 11/106, 6 missing) or *BCR-ABL*-rearrangement (12%, 13/108, 4 missing).

CAR-T treatment and Transplant features

Seventy percent received tisa-cel (79/112), 18% varni-cel (21/112), 4% brexu-cel (4/112), 3% liso-cel (3/112) and 5% an academic product (5/112). At the time of lymphodepletion 14% (15/110, two missing) of patients had EMD involvement, while 43 patients (38%) had morphological disease burden in the bone marrow (>5% blasts).

Overall, 90% (100/111, 1 missing) of patients achieved CR-MRDneg after CAR19 T cell therapy and 7% CR-MRDpos. Eventually, 38% of patients (42/112) experienced disease relapse (including 3 patients who did not reach CR after CAR19 T cells, and one patient with MDS following CAR19 T cell therapy), while an additional 26% (29/112) became MRD positive in morphological CR. One patient developed MDS following CAR19 T cell therapy. Among patients with relapse following CAR19 T-cell therapy, a CD19-negative clone was detected prior to HSCT in 19 of 71 cases (27%).

For the 10% (11/112) of the patients who had active disease upon HSCT, 6% (7/112) had either combined or isolated EMD and 4 had medullary involvement. Among patients in CR upon HSCT, 27/112 (24%) were CR-MRDpos and 65% CR-MRDneg (73/112). Finally, one patient was transplanted in CR after developing MDS.

The conditioning was myeloablative in the majority of patients (87/112, 80%), and most patients received TBI-based conditioning (68/112, 62%). The majority of patients were transplanted by an unrelated donor (53/111, 48%), while 39% (43/111) received an haploidentical HSCT (29 using post-transplant cyclophosphamide platform, 10 using ex vivo T cell depletion, 3 neither *in vivo* nor *ex vivo* T cell depletion, 1 missing). The remaining 13% (15/111) were matched related donors (1 missing HLA details). Extended data on CAR-T and transplant features are summarized in **Table II** and **Table S2**.

Consolidative, pre-emptive, and Rescue HSCT

HSCT was *consolidative* in 19 patients (17%), since these patients were deemed at high risk of relapse due to cytogenetics (n=4), high disease burden before CAR19 T cells (n=11), product out of specification (n=1) or as per institutional standard of care (n=3). A *pre-emptive* transplant was performed in 21 subjects (19%) due to loss of B-cell aplasia (n=17), low/suboptimal CAR19 T cell expansion (n=1), loss of CAR-T cells (n=1), presence of CD19+ hematogones (n=1), pre-CAR19 T cells presence of a CML clone (n=1). The remaining patients (n=72, 64%) received a rescue HSCT due to relapse (n=42), MRD positivity (n=29) or secondary malignancy (MDS, n=1). In this last group (n=69, 3 missing data), 2 patients had never achieved BCA, 11 patients had loss of BCA before relapse/MRD positivity, in 28 the two events occurred simultaneously, while 28 were reported with ongoing B-cell aplasia (12 CD19-negative, 6 EMD, 1 MDS, 9 not specified).

No significant differences were noted between the three groups in terms of median age, distribution of children/adults, CAR19 T cell therapy product, sex, presence of EMD, use of immunotherapy before CAR19 T cells infusion (**Table III**). A higher percentage (68%, 13/19) of patients receiving *consolidative* HSCT had high disease burden before CAR19 T cells infusion, as compared with *rescue* (38%, 27/72) and *pre-emptive* (14%, 3/21) HSCT. Patients receiving a *rescue* HSCT were more frequently already transplant exposed before CAR19 T

cells, when compared with *pre-emptive* and *consolidative* HSCT recipients, respectively (53% vs 29% vs 11%, p = 0.002). While no significant differences were noted in transplant donor, stem cell source and conditioning intensity, a significantly higher proportion of patients receiving *consolidative* HSCT adopted a TBI-based conditioning, when compared with *pre-emptive* and *rescue* HSCT (95% vs 62% vs 54%, p= 0.005). Post-transplant relapse (n=33 events) maintained expression of CD19 in the majority of cases (22/33, 67%), while 30% (10/33) had evidence of CD19-negative disease and one patient had two blast populations (CD19 positive and negative). Four patients had evidence of EMD at relapse post-transplant and no lineage switch was reported. A detailed comparison of the three groups is shown in **Table III** and **Table S3.**

Differences among children and adults

In our cohort, the majority of patients receiving HSCT were children (66%, 74/112, median age 9.5 years, range 1.5-17.99). When compared with adults (34%, 38/112, median age 26 years, range 18.6-67.8) we observed no significant differences in cytogenetic risk, previous transplant history, timing of relapse, timing of HSCT after CAR19 T cells and reason for HSCT. The majority of children (84%, 62/74) received tisa-cel before HSCT, while 56% (21/38) of adults received other types of CAR19 T cell products. A significantly higher percentage of children achieved CR-MRD negative after CAR19 T cells infusion (94% vs 82%, p=0.02), but no significant differences were noted in relapse between CAR19 T cell therapy infusion and HSCT and disease status at the time of transplant. Donor type differed significantly by age group: most adults received unrelated donor grafts (70%; 26/37, 1 missing), whereas haploidentical donors were most frequently used in children (49%; 36/74; p = 0.003). A myeloablative conditioning was used in 90% (67/74) of children (58% in adults, 21/36, 2 missing, p< 0.001), which was TBI-based in 68%, 50/74 (51% adults, 19/36, 1 missing, p= 0.1). Details of comparison between children and adults are shown in **Table IV** and **Table S4**.

Outcome and risk factor analysis

Overall, 38 patients died after HSCT. Thirty-three experienced a disease relapse, at a median time of 4.1 months after transplant. In the whole cohort, the 2-yr OS was 68% and 2-yr LFS was 54%, 2-yr RI was 32%, while 2-yr NRM was 14% (**Figure 1**). Overall, 19 patients died of transplant-related complications: 8 infections, 2 GVHD, 1 GVHD + infection, 1 hemorrhagic event, 2 Transplant-associated thrombotic microangiopathy (TA-TMA), 2 veno-occlusive disease (VOD), 3 unspecified transplant-related complication. 100-day cumulative incidence of Grade II-IV acute GvHD (aGvHD) was 28%, while Grade III-IV aGvHD was 18%. The 2-year cumulative incidence of chronic GvHD (cGvHD) was 24%, while moderate/severe cGvHD was 17%. The composite outcome GRFS in the whole cohort was 38% at 2 years.

Patients receiving a *rescue* HSCT had a significantly lower 2-year LFS (41%), as compared to *pre-emptive* (74%) and *consolidative* HSCT (78%, p= 0.002) (**Figure 2**). The 2-years LFS was 60% vs 42%, for patients transplanted with negative MRD or evidence of disease (either BM or EMD), respectively (p=0.04). Similarly, higher GRFS was noted in patients with CR-MRDneg disease at transplant (44% vs 25%, p=0.009). Conversely, disease status at transplant (CR-MRDneg vs. active disease) showed only a trend towards higher OS (72% vs 60%, p=0.08) and lower RI (27% vs 43%, p=0.08), without significant differences in terms of NRM (13% vs 15%, p= 0.76), respectively.

Children compared with adults showed better OS (75% vs 55%; p=0.02), higher LFS (63% *vs* 38%; p= 0.02), lower RI (25% vs 45%; p= 0.04), but no differences in NRM (12% vs. 17%; p = 0.73) or GRFS (42% vs. 30%, p=0.41)(**Figure 3**).

No significant differences in OS (65% vs 70%, p=0.35), LFS (47% vs 58%, p=0.31), NRM (15% vs 13%, p=0.6) and GRFS (36% vs. 39%, p=0.43) were observed for patients who previously received HSCT before CAR19 T cell therapy versus those who did not, respectively. Similarly, the use of myeloablative conditioning (OS 70% vs 59%, p=0.11; LFS 57% vs 45%, p=0.29; NRM 11% vs 23%, p=0.25) or radiation-based regimen (OS 73% vs 59%, p=0.42; LFS 57% vs 49%,

p=0.72; NRM 11% vs 18%, p=0.78) did not have an impact on transplant outcome. No impact was also observed according to the time elapsing between CAR-T infusion and transplant (**Table S5**).

In multivariable analysis a lower LFS and higher RI were significantly associated with the use of haploidentical donor (LFS HR 2.21, p =0.02; RI HR 2.23, p= 0.049), age at HSCT (LFS HR 1.30, p= 0.01; RI HR 1.32, p = 0.03, HR for 10 years increase) and *rescue* HSCT (LFS HR 4.13, p<0.001; RI HR 8.22, p <0.001). Similarly, worse GRFS was associated with *rescue* HSCT (HR 2.46, p =0.004) and haploidentical donor (HR 1.95, p = 0.02). Conversely, the use of TBI and disease status at transplant did not have an impact on outcomes. Finally, NRM was not significantly associated with age at transplant, reason for HSCT, donor type, disease status and use of TBI (**Table V**).

Discussion

Strategies to prevent relapse in patients with R/R B-ALL receiving CD19-directed CAR-T cell therapies represent a clinical challenge. To date, evidence on the impact of HSCT on large cohorts of patients are lacking and still a certain degree of heterogeneity remains in the indications to proceed to transplant.

Here we report the largest cohort of children and adults with B-ALL that received six different CAR19 T cell products in Europe and subsequently proceeded to HSCT. Given the high-risk features of this selected cohort of patients with B-ALL, our data support an overall favorable outcome of HSCT after CAR19 T cell therapy, with limited treatment-related toxicity, within the expected rate. Importantly, we showed that consolidative or pre-emptive HSCT is associated with favorable outcome, including patients that were transplant-exposed before CAR19 T cell treatment. These differences could be driven by different patient and disease features in the three groups (pre-emptive, consolidative and rescue). However, overall, all the three groups could be

considered at high risk of CAR19 failure due to previous immunotherapy exposure, previous HSCT, high disease burden. Nevertheless, while baseline disease characteristics did not differ significantly, other factors could have contributed to a better outcome observed in the consolidative/pre-emptive group. Firstly, we cannot exclude the possibility of selection bias among patients who underwent HSCT as a consolidative or pre-emptive strategy in patients with highly refractory disease and fit for HSCT. The higher proportion of patients with a history of previous HSCT in the rescue group may reflect an enrichment of more difficult-to-treat B-ALL in this subgroup. Alternatively, it may indicate a lower propensity of treating physicians to offer a second HSCT as a consolidative or pre-emptive strategy, potentially due to comorbidities or concerns regarding the risk of non-relapse mortality (NRM). Similarly, the higher pre-CAR19 disease burden observed in patients who subsequently underwent consolidative HSCT may have been a key factor influencing clinicians' decision to proceed with transplantation. Therefore, we cannot exclude that these differences, rather than the treatment strategy itself, may have contributed, at least in part, to the superior outcomes observed in our study.

In clinical practice, two scenarios identify patients that require careful considerations: a) MRD negative patients with evidence of early loss of BCA or b) MRD negative patients with ongoing BCA and high-risk features. Overall, the optimal duration of persistence of CAR-T cells to prevent relapse is still unclear. Similarly, the lack of expansion of CAR-T after infusion has been associated with rapid disappearance of CAR-T cells, although it remains uncertain if further treatment should be offered to patients with circulating CAR-T cells.

Another significant clinical challenge is represented by the lack of alternative treatment for those who fail CAR-T cell therapy, either for CD19-positive or CD19-negative disease recurrence. Indeed, data on second infusion of CAR19 T cells for treatment of relapse have been disappointing[15-17] and data on CAR22-T cells therapies are only available for small cohorts of patients who can access phase I-II clinical trials[18–20]. Therefore, some expert panels recommend

HSCT in subgroups of patients who are considered at higher risk of relapse, as the most appropriate strategy to consolidate remission and prevent disease recurrence[12].

Our data support the need to better stratify patients according to the risk of relapse. Whether to wait for loss of BCA or to proceed to transplant with circulating CAR-T cells is still debatable and we could observe no difference in terms of outcome between these two approaches. Nevertheless, our data corroborate previous smaller series showing high EFS and OS with consolidative HSCT[21]. A report of 46 children and adults enrolled in clinical trials of CAR19 and CAR22 T cells therapies showed similar OS and EFS rates in transplant-naïve subjects and suggested a negative impact of previous high disease burden and immunotherapies (e.g. blinatumomab and inotuzumab) on transplant outcome[4], that was not observed in our larger cohort.

Importantly, we compared outcomes according to previous exposure to HSCT and we could detect no difference in terms of OS, NRM and GRFS, suggesting that second procedures after CAR-T cell therapy are not affected by a higher degree of toxicity that should contraindicate this strategy in previously transplanted patients. We acknowledge that the decision to proceed to second HSCT needs to be driven by several patients' characteristics (timing from previous transplant, myeloablative conditioning, performance status, donor type and availability) and should be a tailored strategy. However, the NRM <20% in both allo-naïve and allo-exposed groups supports the decision to offer transplant also in highly pre-treated patients, despite a previous transplant procedure. This is corroborated by our observation that use of TBI or myeloablative conditioning had no significant impact on transplant outcome in terms of OS, LFS and NRM. In a cohort of 45 adults undergoing a consolidative HSCT after CAR19 T cell therapy, NRM and RFS rates were similar in those who received a first or a second allo-HSCT, and, similarly to our cohort, only a subset of patients received radiation-based myeloablative conditioning[22]. By contrast, a previous report of a smaller cohort of patients suggests that the

clinical benefit of consolidative second transplant after CAR19 T cells infusion[23] is limited to patients with very early (< 60 days) loss of CAR-T cells. To date, it remains unclear if second transplant should be offered only in case radiation-based myeloablation could be used and which is the most appropriate donor (e.g. haploidentical to elicit graft versus leukemia effect; other matched donor).

In our cohort, the majority of patients that received HSCT after CAR-T were children, possibly reflecting the fact that younger patients will more likely proceed to transplant, especially if not previously allo-exposed, given the lower burden of co-morbidities. Of note children more likely received myeloablative conditioning, which might have had an impact on the higher LFS and lower RI (although not confirmed in multivariable analysis) observed in younger patients, including a lower percentage of MRD positive patients at transplant. However, the similar NRM among the groups suggest that the main limitation of HSCT after CAR19 T cell in adults is represented by the higher risk of relapse, also considering the higher percentage of transplant-exposed patients in the adult group. Therefore, in this population, less intense leukemia therapy to reduce MRD level or use of non-myeloablative conditioning to avoid toxicity should be carefully balanced with the risk of transplant failure due to relapse. Meaningful separate analysis for children and adults were not feasible due to the limited number of patients, especially in the adult cohort. Therefore, we cannot exclude that the predominance of subjects receiving myeloablative conditioning (particularly TBI), who were transplant naïve and MRD negative at transplant in the pediatric sub-group could have contributed to the observed better outcome.

Finally, the multivariable analysis confirmed that outcome of HSCT after CAR19 T cell therapies was mainly affected by the recurrence of disease before transplant (rescue HSCT vs consolidative/pre-emptive HSCT) and age at the time of transplant, possibly supporting an early intervention approach in children considered at high risk of relapse. The prognostic outlook appears also to be influenced by donor type. Of note, the higher RI with haploidentical donors

(mainly adopting post-transplant cyclophosphamide) challenge the concept to elicit graft versus leukemia with mismatched donors, as additional strategy to prevent disease relapse after transplant. However, since this association resulted at the limit of significance (p=0.049, HR 2.23, 95%CI 1.01-4.95) and given the heterogeneity of haplo-transplant platforms and the limited numbers of patients, further sub-analysis on *ex vivo* or *in vivo* T cell depletion were not feasible. Conversely, MRD negativity did not appear to be associated with a favorable outcome. Although CR MRD negativity at transplantation was positively associated with LFS and GRFS in the univariate analysis, this association was not confirmed in the multivariable analysis. We cannot exclude the possibility that the association between CR MRD negativity and HCT indication may have influenced these findings, particularly as the reason has a significant impact in the multivariable analysis. Moreover, statistical interaction terms between HCT indication and the other covariates (age at HCT, disease status at HCT, donor type, and TBI) were tested in the multivariable model for LFS; none of the interaction terms was statistically significant.

This is indeed in contrast with the experience in FORUM trial for paediatric B-ALL patients receiving matched donor HSCT, where pre-HSCT MRD <0.01% was associated with lower risk of RI[24], while the level of positivity did not affect the outcome. However, the limited number of patients with active disease at transplant (including patients with EMD) and the heterogeneity of MRD monitoring assays in our study prevent further generalization.

Other groups have proposed different strategies to prevent relapse in previously transplanted patients including second CAR19 T cells infusion[15] or maintenance chemotherapy[25]. While setting up a prospective randomized study in such small groups of patients is challenging, larger collaborative retrospective study could be warranted to compare different approaches to prevent disease relapse after CAR19 T cells therapies in R/R B-ALL patients.

We acknowledge the main limitations of this study, related to its retrospective nature: (1) heterogeneity of CAR19 T cell products: different anti-CD19 CAR-T constructs (4-1BB or

CD28 co-stimulatory domains) associated with different persistence kinetics might prevent generalization over the opportunity to proceed to consolidative/pre-emptive HSCT; ; (2) bias in offering pre-emptive/consolidative transplant according to fitness of patients, refractoriness of disease, high disease burden; (3) limited number of subjects across the sub-groups: this prevented the characterization of the risk profile. Furthermore, the pre-emptive group included heterogenous indications to HSCT, that might prevent generalization on this approach in all the clinical scenario included in this sub-group.

Another source of heterogeneity is the variability in post-CAR-T monitoring strategies across centers. MRD monitoring was performed according to local policies, using different assays, including flow cytometry and PCR. Similarly, CAR-T persistence and BCA loss may have been defined differently across centers and assessed using different methodologies. Consequently, the clinical approach to this scenario may also vary substantially among centers, for instance because of different thresholds used to define loss of BCA. Finally, comparison with non-transplanted CAR19 T cells recipients, especially those with recurrent disease not achieving remission, is not provided. Such an analysis in a retrospective study would be subject to the same limitations discussed above, including heterogeneity in the criteria for offering HSCT after CAR19 T cell therapy. Moreover, prospective randomized trials are extremely challenging to conduct in this patient population. A retrospective study involving more than 200 patients used propensity score matching to mitigate baseline confounding and compare outcomes between adult recipients of CD19-directed CAR T-cell therapy who underwent consolidative HSCT and those who did not. The study reported improved overall survival (OS) and relapse-free survival (RFS) among patients who received consolidative HSCT[26]. Conversely, the real-world data on >700 patients receiving tisa-cel in B-ALL reported by *John et al.* suggest that, after CAR19 T cell therapy, HSCT has a general limited impact on outcome, with no significant difference in RFS when censoring or not censoring for HSCT, in both children and adults[2]. Although this represents the

largest dataset of patients receiving tisa-cel, the lack of sub-stratification regarding reason for HSCT, MRD status, previous therapies and disease features prevent further generalization. Future large-scale collaborative efforts should aim to address this important question by comparing patients who undergo HSCT after CAR-T cell therapy with those who do not proceed to transplantation as a consolidation or pre-emptive strategy.

Despite these limitations, here we report the largest cohort of patients receiving allogeneic HSCT after CAR19 T cells therapies for B-ALL. We showed that HSCT could offer a high OS in heavily pre-treated patients, that in most cases have exhausted other possible therapeutic options. Our study shows that consolidative and pre-emptive HSCT are associated with a high rate of success, especially in children, irrespective of previous transplant exposure and the conditioning used. Previous transplant exposure should be carefully considered and the decision to proceed to second HSCT should take into account timing elapsed between the first and second procedure, history of GvHD or previous severe transplant-related toxicities, different HLA matching/donor type. However, in selected patients second HSCT represents a viable curative option, once remission is achieved after CAR19 T cells therapy, especially if the patient has already failed other conventional therapy.

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Tables

Table I. Demographics, clinical and disease features of 112 patients receiving HSCT after CAR19 T cell therapies. *Abbreviations: HSCT: hematopoietic stem cell transplantation.*

^including one patient with MDS

Variables		**N=112 (%)**
Patient sex	Female	46 (41.1)
	Male	66 (58.9)
Age at HSCT	median [IQR]	13.9 [8.3-22.5]
Age at HSCT (< or ≥ 18 yo)	Adult	38 (33.9)
	Child	74 (66.1)
Disease risk at diagnosis	standard	63 (67.7)
	high	30 (32.3)
	missing	19
Allo HSCT before CAR19 T cell therapy	No	66 (58.9)
	Yes	46 (41.1)
Years between HSCT before CAR19 T cell therapy and this HSCT	median [IQR]	2.5 [1.8-3.7]
Months from CAR19 T cell therapy to HSCT	median [IQR]	6.1 [3.7-12.9]
Relapse before allo-HSCT	No relapse	41 (36.6)
	Molecular relapse	29 (25.9)
	Relapse	42 (37.5)^

Table II. CAR19 T cell therapy and transplant features of 112 patients receiving HSCT after CAR19 T cell therapies. *Abbreviations: BCA: B-cell aplasia; BM: bone marrow; CB: cord blood; CNS: central nervous system; CR: complete remission; EMD: extra-medullary disease; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; MRD: minimal residual disease; PB: peripheral blood; TBI: total body irradiation; UD: unrelated donor.*

Variables		N=112 (%)
Reason of the HSCT	Consolidative	19 (17)
	Pre-emptive	21 (18.8)
	Hematological relapse	42 (37.5)
	HSCT for secondary malignancy (MDS) post CAR19 T cell therapy	1 (0.9)
	Molecular relapse	29 (25.9)
CAR19 T cell therapy product	Tisa-cel (Kymriah)	79 (70.5)
	Varni-cel (ARI-0001)	21 (18.8)
	Liso-cel (Breyanzi)	3 (2.7)
	Sheba CAR19 T cell therapy	4 (3.6)
	Brexu-cel (Tecartus)	4 (3.6)
	Tuebingen CAR19 T cell therapy	1 (0.9)
Disease status at HSCT	CR MRD neg	73 (65.2)
	CR MRD pos	27 (24.1)
	CNS isolated	4 (3.6)
	Including EMD (Bone + Other)	1 (0.9)
	Node isolated	1 (0.9)
	Spleen isolated	1 (0.9)
	Non-CR	4 (3.6)
	CR (MDS)	1 (0.9)
HSCT Donor type	Matched relative (non haplo)	15 (13.5)
	Mismatched relative (haplo)	43 (38.7)
	UD	53 (47.7)
	missing	1
HSCT Source	BM	30 (27.5)
	PB	76 (69.7)
	CB	2 (1.8)
	Double CB	1 (0.9)
	missing	3
Myeloablative regimen	No	22 (20.2)
	Yes	87 (79.8)
	missing	3
TBI-based regimen	No	42 (38.2)
	Yes	68 (61.8)
	missing	2

Table III. Comparison of patients, disease and transplant characteristics among 3 groups of patients, according to the reason of performing HSCT (pre-emptive, consolidative, rescue), as mentioned in the methods section. Analysis was performed using X^2 test or student T test. Significant p values (<0.05) are reported in red. *Abbreviations: BM: bone marrow; CB: cord blood; CNS: central nervous system; CR: complete remission; EMD: extra-medullary disease; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; MRD: minimal residual disease; PB: peripheral blood; TBI: total body irradiation; UD: unrelated donor.*

Variables	Modalities	Consolidative (N=19)	Preemptive (N=21)	Rescue (N=72)	p value
Age at this HSCT	median [IQR]	13 [8.3-23.3]	12 [8.1-17.9]	15.6 [8.4-23.2]	0,62
	(range)	(4.2-49.1)	(1.5-45.4)	(2.5-67.8)	
Age at this HSCT	Adult	7 (36.8)	5 (23.8)	26 (36.1)	0,55
	Child	12 (63.2)	16 (76.2)	46 (63.9)	
Allo HSCT before CAR19 T cell therapy	No	17 (89.5)	15 (71.4)	34 (47.2)	0,002
	Yes	2 (10.5)	6 (28.6)	38 (52.8)	
Months from HSCT1 to relapse before CAR19 T cell therapy	No prev HSCT	17 (89.5)	15 (71.4)	34 (47.2)	0.03
	(0,6]	0 (0)	0 (0)	8 (11.3)	
	(6,12]	0 (0)	1 (4.8)	11 (15.5)	
	(12,48]	2 (10.5)	5 (23.8)	18 (25.4)	
	missing	0	0	1	
CAR19 T cell therapy	Tisa-cel (Kymriah)	15 (78.9)	13 (61.9)	51 (70.8)	Not done
	Varni-cel (ARI-0001)	0 (0)	6 (28.6)	15 (20.8)	
	Liso-cel (Breyanzi)	0 (0)	1 (4.8)	2 (2.8)	
	Sheba CAR19 T cell therapy	2 (10.5)	0 (0)	2 (2.8)	
	Brexu-cel (Tecartus)	2 (10.5)	1 (4.8)	1 (1.4)	
	Tuebingen CAR19 T cell therapy	0 (0)	0 (0)	1 (1.4)	
Months first CAR19 T cell therapy to HSCT	median [IQR]	3.5 [2.7-4.2]	4.4 [3.4-5.6]	9.5 [5.7-17.2]	< 0.001
Response after CAR19 T cell therapy	CR MRD neg	19 (100)	21 (100)	60(84.5)	0.22
	CR MRD pos	0 (0)	0 (0)	8 (11.3)	
	No CR	0 (0)	0 (0)	3 (4.2)	
	missing	0	0	1	
Disease status at HSCT	CR MRD neg	18 (94.7)	20 (95.2)	35 (48.6)	Not done
	CR MRD pos	1 (5.3)	1 (4.8)	25 (34.7)	
	CNS isolated	0 (0)	0 (0)	4 (5.6)	
	Including EMD (Bone + Other)	0 (0)	0 (0)	1 (1.4)	
	Node isolated	0 (0)	0 (0)	1 (1.4)	
	Spleen isolated	0 (0)	0 (0)	1 (1.4)	
	BM Non-CR	0 (0)	0 (0)	4 (5.6)	
	CR (MDS)	0 (0)	0 (0)	1 (1.4)	
Donor type	Matched relative	3 (15.8)	5 (23.8)	7 (9.9)	0.36
	Mismatched relative	9 (47.4)	8 (38.1)	26 (36.6)	
	UD	7 (36.8)	8 (38.1)	38 (53.5)	
	missing	0	0	1	
Myeloablative regimen	No	1 (5.3)	3 (14.3)	18 (25.7)	0.12
	Yes	18 (94.7)	18 (85.7)	52 (74.3)	

	missing	0	0	2	
TBI regimen	No	1 (5.3)	8 (38.1)	33(46.4)	0.005
	Yes	18 (94.7)	13 (61.9)	38 (53.5)	
	missing	0	0	1	

Table IV. Post-CAR-T HSCT comparison of patients, disease and transplant characteristics among children and adults. Analysis was performed using X^2 test or student T test. Significant p values (<0.05) are reported in red. *Abbreviations: BCA: B-cell aplasia; BM: bone marrow; CB: cord blood; CNS: central nervous system; CR: complete remission; EMD: extra-medullary disease; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; MRD: minimal residual disease; PB: peripheral blood; TBI: total body irradiation; UD: unrelated donor.*

Variables	Modalities	Adult (N=38)	Child (N=74)	p value
Reason of the HSCT	Consolidative	7 (18.4)	12 (16.2)	0.09
	Preemptive	5 (13.2)	16 (21.6)	
	Hemato relapse	19 (50)	23 (31.1)	
	HSCT for secondary malignancy (MDS) post CAR19 T cell therapy	1 (2.6)	0 (0)	
	Mol relapse	6 (15.8)	23 (31.1)	
HSCT before CAR19 T cell therapy	No	18 (47.4)	48 (64.9)	0.07
	Yes	20 (52.6)	26 (35.1)	
CAR19 T cell therapy	Tisa-cel (Kymriah)	17 (44.7)	62 (83.8)	Not done
	Varni-cel (ARI-0001)	12 (31.6)	9 (12.2)	
	Liso-cel (Breyanzi)	0 (0)	3 (4.1)	
	Sheba CAR19 T cell therapy	4 (10.5)	0 (0)	
	Brexu-cel (Tecartus)	4 (10.5)	0 (0)	
	Tuebingen CAR19 T cell therapy	1 (2.6)	0 (0)	
Months first CAR19 T cell therapy to HSCT	median [IQR]	6.8 [4.3-15.5]	6 [3.7-11]	0.25
Response after CAR19 T cell therapy	CR MRD neg	31 (81.6)	69 (94.5)	**0.02**
	CR MRD pos	4 (10.5)	4 (5.5)	
	No CR	3 (7.9)	0 (0)	
	missing	0	1	
Relapse before alloHSCT	No relapse	13 (34.2)	28 (37.8)	0.09
	Mol relapse	6 (15.8)	23 (31.1)	
	Relapse	19 (50)	23 (31.1)	
Disease status at HSCT	CR MRD neg	20 (52.6)	53 (71.6)	Not done
	CR MRD pos	13 (34.2)	14 (18.9)	
	CNS isolated	2 (5.3)	2 (2.7)	
	Including EMD (Bone+Other)	1 (2.6)	0 (0)	
	Node isolated	0 (0)	1 (1.4)	
	Non-CR	1 (2.6)	3 (4.1)	
	Spleen isolated	0 (0)	1 (1.4)	
	CR (MDS)	1 (2.6)	0 (0)	
Donor type	Matched relative	4 (10.8)	11 (14.9)	**0.003**
	Mismatched relative	7 (18.9)	36 (48.6)	
	UD	26 (70.3)	27 (36.5)	
	missing	1	0	
Source of cells	BM	3 (8.1)	26 (35.6)	**0.002**
	PB	32(86.5)	46 (63)	
	CB	1 (2.7)	1 (1.4)	
	Double CB	1 (2.7)	0 (0)	
	missing	1	1	
Myeloablative regimen	No	15 (41.7)	7 (9.5)	**< 0.001**
	Yes	21 (58.3)	67 (90.5)	

	missing	2	0	
TBI regimen	No	18 (48.6)	24 (32.4)	0.1
	Yes	19 (51.4)	50 (67.6)	
	missing	1	0	

Table V. Cox proportional hazards regression model for multivariable analysis of clinically relevant risk factors for LFS, OS, RI, NRM and GRFS. Significant p values (<0.05) are reported in red.

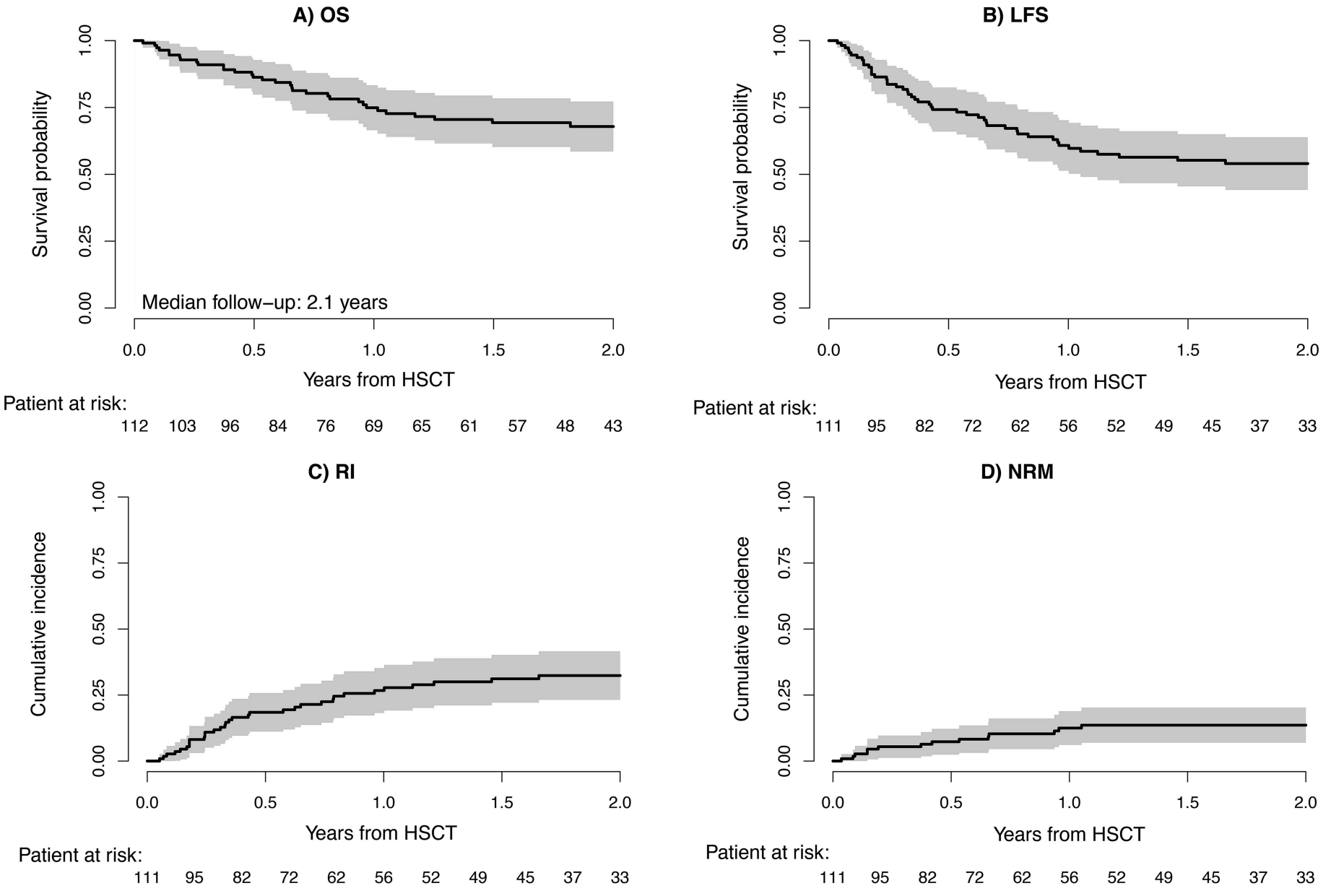
		LFS		OS		RI		NRM		GRFS	
Variables	**Modalities**	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**
Age (HR for 10y inc)		1.30 (1.06-1.61)	0.01	1.27 (1.01-1.59)	0.04	1.32 (1.03-1.69)	0.03	1.28 (0.87-1.90)	0.21	1.13 (0.94-1.36)	0.21
Reason for HCT	Not rescue	1		1		1		1		1	
	Rescue	4.13 (1.90-8.97)	< 0.001	3.16 (1.29-7.77)	0.01	8.22 (2.67-25.31)	< 0.001	1.56 (0.47-5.15)	0.47	2.46 (1.34-4.54)	0.004
Donor type	Not Haplo	1		1		1		1		1	
	Haplo	2.21 (1.15-4.25)	0.02	2.07 (0.99-4.27)	0.051	2.23 (1.01-4.95)	0.049	2.25 (0.72-7.04)	0.16	1.95 (1.13-3.37)	0.02
Disease status at HCT	CR MRD neg	1		1		1		1		1	
	Not CR MRD neg	0.95 (0.49-1.84)	0.88	0.92 (0.43-1.95)	0.83	0.92 (0.42-2.00)	0.83	1.02 (0.28-3.67)	0.98	1.34 (0.76-2.35)	0.31
Use of TBI	No	1		1		1		1		1	
	Yes	1.61 (0.85-3.02)	0.14	1.10 (0.56-2.16)	0.78	1.88 (0.87-4.07)	0.11	1.19 (0.40-3.56)	0.76	1.40 (0.82-2.40)	0.22

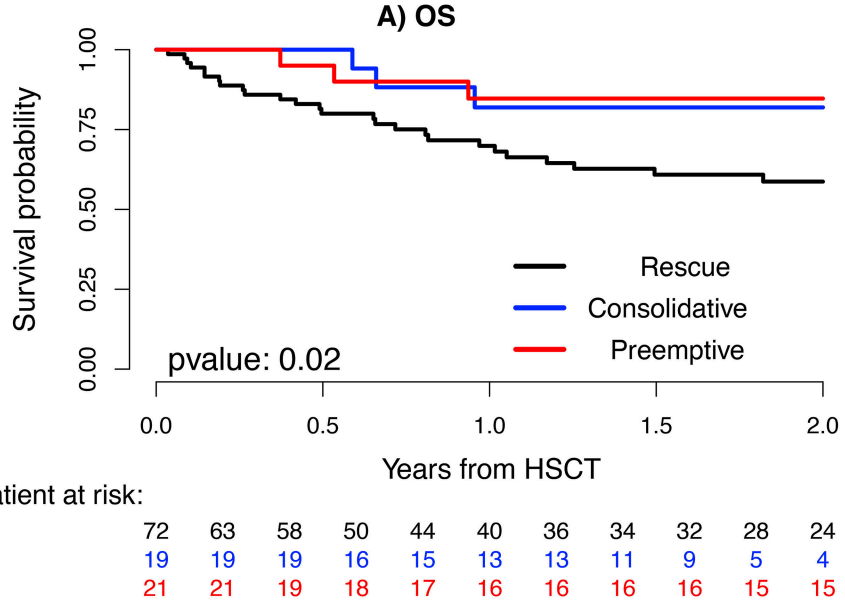
Figures

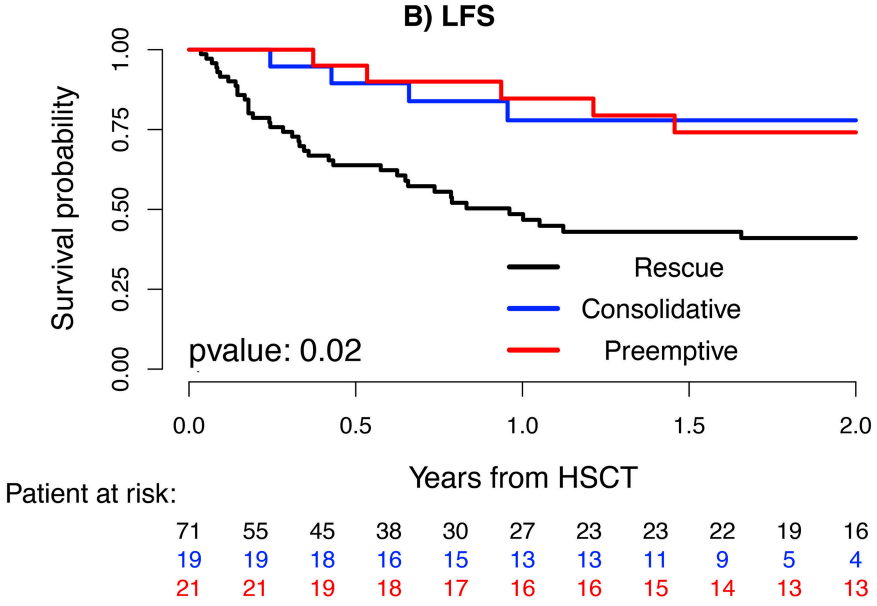
Figure 1. Outcome of 112 patients receiving HSCT after CAR19 T cell therapy. *Kaplan–Meier curves display 2-year overall survival (A), 2-year leukemia-free survival (B), while cumulative incidence curves show 2-year relapse incidence (C), and 2-year non-relapse mortality incidence (D). Abbreviations: OS: overall survival; LFS: leukemia free survival; RI: relapse incidence; NRM: non-relapse mortality*

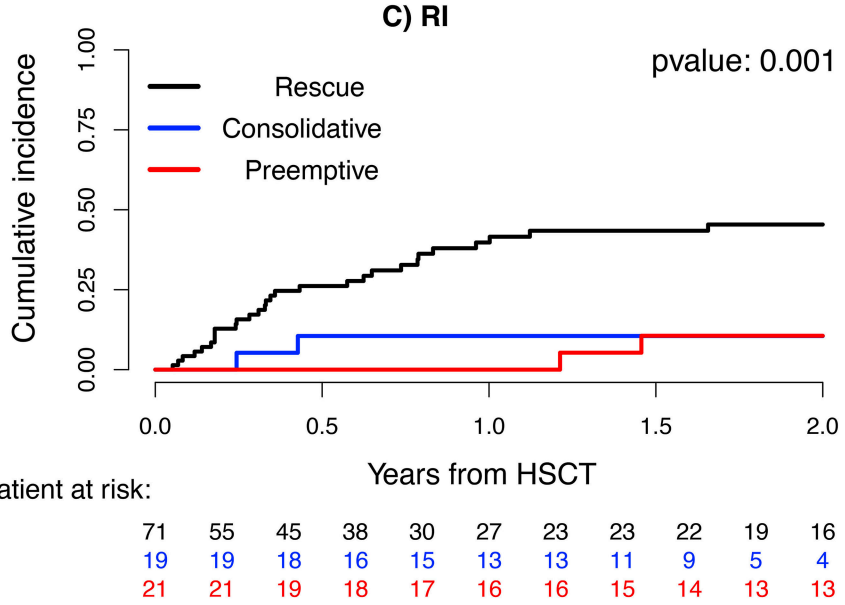
Figure 2. Outcome of patients receiving HSCT after CAR19 T cell therapy according to the reason for HSCT. *Kaplan–Meier curves show 2-year overall survival (A) and 2-year leukemia free survival (B), while cumulative incidence curves show 2-year relapse incidence (C), and 2-year non-relapse mortality incidence (D), stratified into three groups: pre-emptive (red line), consolidative (blue line), rescue (black line). Abbreviations: OS: overall survival; LFS: leukemia free survival; RI: relapse incidence; NRM: non-relapse mortality*

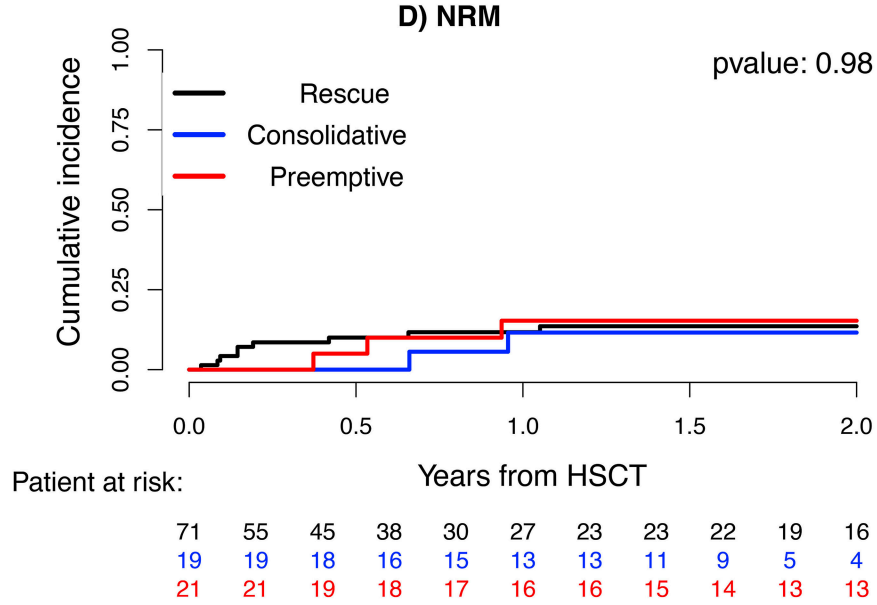
Figure 3. Outcome of patients receiving HSCT after CAR19 T cell therapy according to the age. *Kaplan–Meier curves show 2-year overall survival (A) and 2-year leukemia free survival (B), while cumulative incidence curves show 2-year relapse incidence (C), and 2-year non-relapse mortality incidence (D), comparing children (blue line) and adults (black line). Abbreviations: OS: overall survival; LFS: leukemia free survival; RI: relapse incidence; NRM: non-relapse mortality*

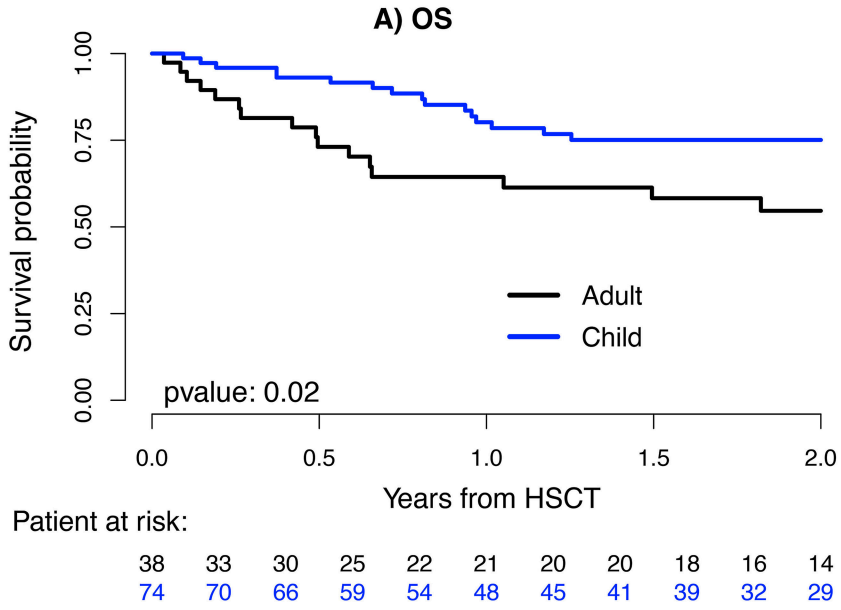

A) OS
Survival probability
1.00
0.75
0.50
0.25
0.00
Median follow−up: 2.1 years
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
112 103 96 84 76 69 65 61 57 48 43
B) LFS
Survival probability
1.00
0.75
0.50
0.25
0.00
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
111 95 82 72 62 56 52 49 45 37 33
C) RI
Cumulative incidence
1.00
0.75
0.50
0.25
0.00
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
111 95 82 72 62 56 52 49 45 37 33
D) NRM
Cumulative incidence
1.00
0.75
0.50
0.25
0.00
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
111 95 82 72 62 56 52 49 45 37 33

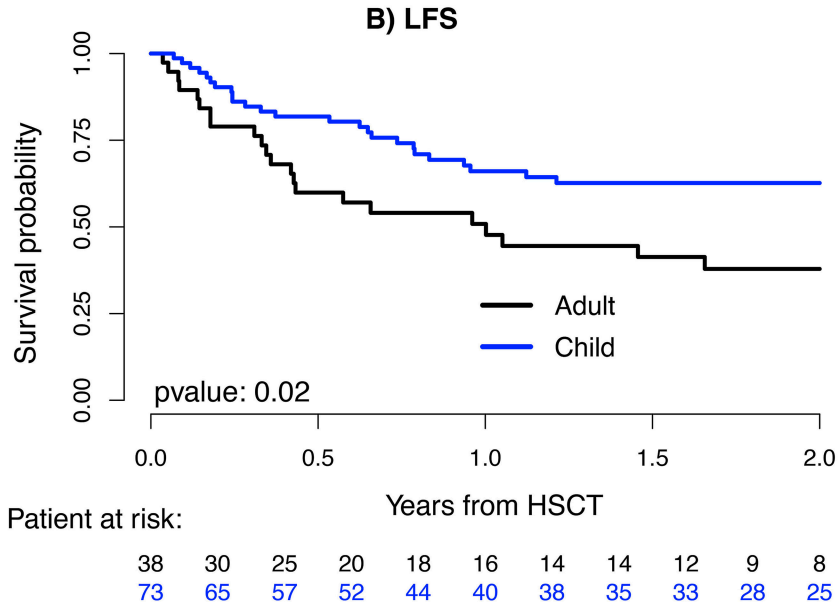

A) OS
Survival probability
0.00
0.25
0.50
0.75
1.00
pvalue: 0.02
Rescue
Consolidative
Preemptive
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
72 63 58 50 44 40 36 34 32 28 24
19 19 19 16 15 13 13 11 9 5 4
21 21 19 18 17 16 16 16 16 15 15

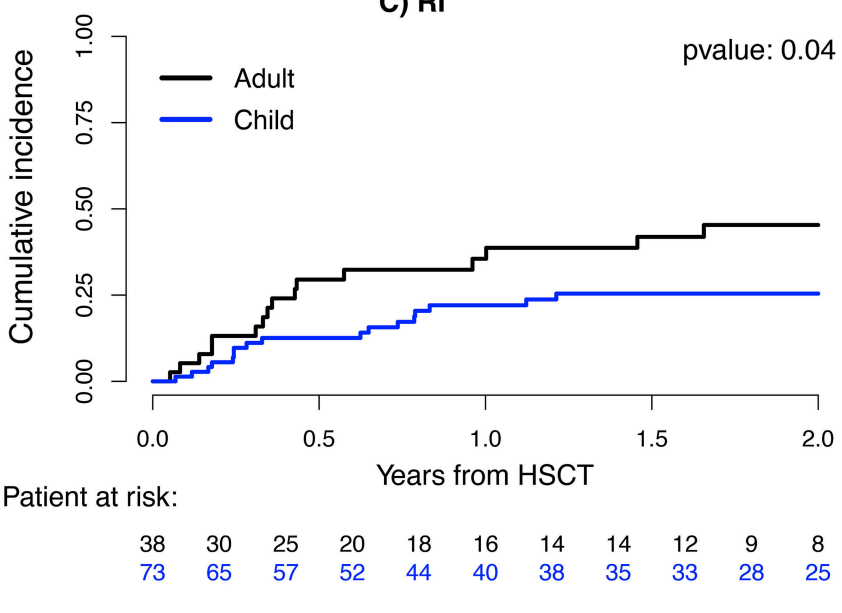

B) LFS
Survival probability
0.00
0.25
0.50
0.75
1.00
pvalue: 0.02
Rescue
Consolidative
Preemptive
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
71 55 45 38 30 27 23 23 22 19 16
19 19 18 16 15 13 13 11 9 5 4
21 21 19 18 17 16 16 15 14 13 13

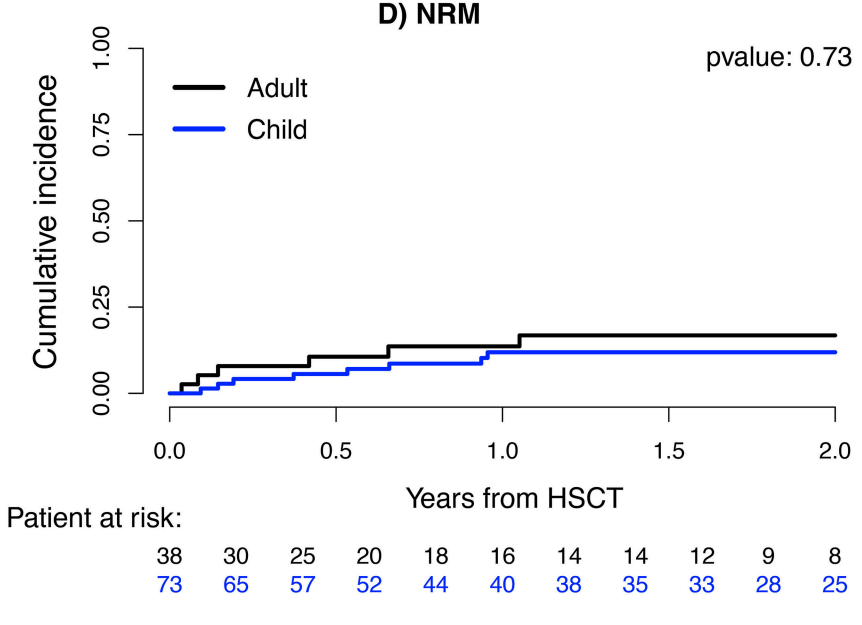

C) RI
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
pvalue: 0.001
Rescue
Consolidative
Preemptive
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
71 55 45 38 30 27 23 23 22 19 16
19 19 18 16 15 13 13 11 9 5 4
21 21 19 18 17 16 16 15 14 13 13


D) NRM
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
pvalue: 0.98
Rescue
Consolidative
Preemptive
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
71 55 45 38 30 27 23 23 22 19 16
19 19 18 16 15 13 13 11 9 5 4
21 21 19 18 17 16 16 15 14 13 13


A) OS
Survival probability
0.00
0.25
0.50
0.75
1.00
Adult
Child
pvalue: 0.02
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
38 33 30 25 22 21 20 20 18 16 14
74 70 66 59 54 48 45 41 39 32 29


B) LFS
Survival probability
0.00
0.25
0.50
0.75
1.00
Adult
Child
pvalue: 0.02
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
38 30 25 20 18 16 14 14 12 9 8
73 65 57 52 44 40 38 35 33 28 25


C) RI
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
pvalue: 0.04
Adult
Child
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
38 30 25 20 18 16 14 14 12 9 8
73 65 57 52 44 40 38 35 33 28 25


D) NRM
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
pvalue: 0.73
Adult
Child
0.0
0.5
1.0
1.5
2.0
Years from HSCT
Patient at risk:
38 30 25 20 18 16 14 14 12 9 8
73 65 57 52 44 40 38 35 33 28 25

Supplementary Materials

Table S1. Details and additional disease characteristics of 112 patients receiving HSCT after CAR19 T cell therapy. *Abbreviations: ALL: acute lymphoblastic leukemia; CNS: central nervous system; CR: complete remission; EMD: extra-medullary disease; HSCT: hematopoietic stem cell transplantation; Mol: molecular; MRD: minimal residual disease.*

Variables		N= 112 (100%)
EMD at ALL diagnosis	No	90 (81.8)
	CNS	10 (9.1)
	CNS+Facial nerve	1 (0.9)
	CNS+Testis	1 (0.9)
	CNS+Testis+Kidney+Bone+Nodes	1 (0.9)
	Bone	4 (3.6)
	Kidney	1 (0.9)
	Lytic	1 (0.9)
	Node	1 (0.9)
	missing	2
BCR-ABL	No	95 (88)
	Yes	13 (12)
	missing	4
MLL	No	95 (89.6)
	Yes	11 (10.4)
	missing	6
Number of alloHSCT before CAR-T	0	66 (58.9)
	1	44 (39.3)
	2	2 (1.8)
Months from HSCT to relapse before CAR-T	No prev HSCT	66 (59.5)
	(0,6]	8 (7.2)
	(6,12]	12 (10.8)
	(12,48]	25 (22.5)
	missing	1
Characterization of the relapse before HSCT	No relapse	41 (36.6)
	Molecular relapse	29 (25.9)
	Progression/Hematological Relapse	27 (24.1)
	CNS +/- BM	8 (7.1)
	EMD (not CNS) +/- BM	7 (6.3)

Table S2. Details and additional patients, CAR19 T cell therapy and transplant characteristics of 112 patients receiving HSCT after CAR19 T cell therapy. *Abbreviations: UCB: umbilical cord blood; CML: chronic myeloid leukemia; CNS: central nervous system; CR: complete remission; EMD: extra-medullary disease; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; MRD: minimal residual disease; UD: unrelated donor.*

Variables		**N= 112 (100%)**
HSCT planned before CAR-T	No	76 (69.7)
	Yes	33 (30.3)
	missing	3
Second CAR19 T cell infusion between first CAR19 T cell therapy and this HSCT	Yes	17 (15.2)
	No	95 (84.8)
B-cell aplasia	BCA not reached	2 (1.9)
	BCA loss	57 (53.2)
	BCA ongoing	48 (44.9)
	missing	5
Reason of the HSCT (detailed)	High-risk cytogenetics/mutations (before CAR-T)	4 (3.6)
	High disease burden (before CAR-T)	11 (9.8)
	Product out-of-specification	1 (0.9)
	Standard of care	3 (2.7)
	Loss of B-cell aplasia	17 (15.2)
	Low/suboptimal CAR-T expansion	1 (0.9)
	CAR-T Non permanent	1 (0.9)
	CD19 Hematogones	1 (0.9)
	CML clone	1 (0.9)
	Hematological relapse (after CAR-T)	42 (37.5)
	MRD+ (after CAR-T)	29 (25.9)
	HSCT for secondary malignancy (MDS) post CAR-T	1 (0.9)
EMD at apheresis	No	79 (73.1)
	CNS	15 (13.9)
	CNS+Optic Nerve	3 (2.8)
	CNS+Testis	1 (0.9)
	Bone	3 (2.8)
	Breast+Kidney+Bone	1 (0.9)
	Cutaneous	2 (1.9)
	Lytic	1 (0.9)
	Node	1 (0.9)
	Testis	1 (0.9)
	Testis+Kidney+Bone	1 (0.9)
	missing	4
EMD at lymphodepletion	No	95 (86.4)

	CNS	2 (1.8)
	CNS+Cutaneous	1 (0.9)
	CNS+Facial nerve	1 (0.9)
	Bone	6 (5.5)
	Breast+Pancreas+Nodes	1 (0.9)
	Cutaneous	1 (0.9)
	Lytic	1 (0.9)
	Node	1 (0.9)
	Uterus	1 (0.9)
	missing	2
Donor type (detailed)	Identical sibling	12 (10.8)
	Matched other relative	2 (1.8)
	Mismatched relative 1 locus	1 (0.9)
	Haploidentical HSCT	43 (38.7)
	UD 10/10	29 (26.1)
	UD 9/10	18 (16.2)
	UD 8/10	1 (0.9)
	UD (HLA missing)	2 (1.8)
	UCB 5/6	1 (0.9)
	UCB (missing HLA)	1 (0.9)
	Double UCB	1 (0.9)
	missing	1

Table S3. Details and additional patients, disease and transplant characteristics of patients receiving pre-emptive or consolidative or rescue HSCT after CAR19 T cell therapy. *Abbreviations: CART2: second CAR-T cell infusion; CB: cord blood; CML: chronic myeloid leukemia; CNS: central nervous system; CR: complete remission; EMD: extra-medullary disease; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; Mol: molecular; MRD: minimal residual disease; UD: unrelated donor.*

Variables		Consolidative (N=19)	Preemptive (N=21)	Rescue (N=72)	P value
Patient sex	Female	8 (42.1)	9 (42.9)	29 (40.3)	0.97
	Male	11 (57.9)	12 (57.1)	43 (59.7)	
Disease risk at diagnosis	standard	13 (72.2)	9 (60)	41 (68.3)	0.73
	high	5 (27.8)	6 (40)	19 (31.7)	
	missing	1	6	12	
HSCT planned before CAR-T	No	1 (5.3)	15 (71.4)	60 (87)	**<0.001**
	Yes	18 (94.7)	6 (28.6)	9 (13)	
	missing	0	0	3	
Years first HSCT before CAR19 T cell therapy and this HSCT	median [IQR]	3.3 [3.1-3.6]	1.9 [1.7-2.3]	2.6 [1.9-3.8]	Not done
	(range)	(2.8-3.8)	(0.8-3.5)	(1.1-6.2)	
Reason of the HSCT	High-risk cytogenetics/mutations (before CAR-T)	4 (21.1)			Not done
	High disease burden (before CAR-T)	11 (57.9)			
	Product out-of-specification	1 (5.3)			
	Standard of care	3 (15.8)			
	Loss of B-cell aplasia		17 (81)		
	Low/suboptimal CAR19 T cell expansion		1 (4.8)		
	CAR-T Non permanent		1 (4.8)		
	CD19 Hematogones		1 (4.8)		
	CML clone		1 (4.8)		
	Hematological relapse (after CAR-T)			42 (58.3)	
	MRD+ (after CAR-T)			29 (40.3)	
	HSCT for secondary malignancy (MDS) post CAR-T			1 (1.4)	

EMD at ALL diagnosis	No	16 (84.2)	20 (95.2)	54 (77.1)	Not done
	CNS	1 (5.3)	1 (4.8)	8 (11.4)	
	CNS+Facial nerve	0 (0)	0 (0)	1 (1.4)	
	CNS+Testis	0 (0)	0 (0)	1 (1.4)	
	CNS+Testis+Kidney+Bone+Nodes	0 (0)	0 (0)	1 (1.4)	
	Bone	0 (0)	0 (0)	4 (5.7)	
	Kidney	0 (0)	0 (0)	1 (1.4)	
	Lytic	1 (5.3)	0 (0)	0 (0)	
	Node	1 (5.3)	0 (0)	0 (0)	
	missing	0	0	2	
BCR-ABL	No	14 (77.8)	19 (90.5)	62 (89.9)	0.38
	Yes	4 (22.2)	2 (9.5)	7 (10.1)	
	missing	1	0	3	
MLL	No	18 (100)	18 (90)	59 (86.8)	0.34
	Yes	0 (0)	2 (10)	9 (13.2)	
	missing	1	1	4	
EMD at CAR-T apheresis	No	14 (73.7)	16 (76.2)	49 (72.1)	Not done
	CNS	1 (5.3)	4 (19)	10 (14.7)	
	CNS+Optic Nerve	1 (5.3)	1 (4.8)	1 (1.5)	
	CNS+Testis	0 (0)	0 (0)	1 (1.5)	
	Bone	0 (0)	0 (0)	3 (4.4)	
	Breast+Kidney+Bone	0 (0)	0 (0)	1 (1.5)	
	Cutaneous	1 (5.3)	0 (0)	1 (1.5)	
	Lytic	1 (5.3)	0 (0)	0 (0)	
	Node	1 (5.3)	0 (0)	0 (0)	
	Testis	0 (0)	0 (0)	1 (1.5)	
	Testis+Kidney+Bone	0 (0)	0 (0)	1 (1.5)	
	missing	0	0	4	
EMD at CAR-T lymphodepletion	No	17 (89.5)	21 (100)	57 (81.4)	Not done
	CNS	0 (0)	0 (0)	2 (2.9)	
	CNS+Cutaneous	1 (5.3)	0 (0)	0 (0)	
	CNS+Facial nerve	0 (0)	0 (0)	1 (1.4)	
	Bone	0 (0)	0 (0)	6 (8.6)	
	Breast+Pancreas+Nodes	0 (0)	0 (0)	1 (1.4)	
	Cutaneous	0 (0)	0 (0)	1 (1.4)	
	Lytic	1 (5.3)	0 (0)	0 (0)	
	Node	0 (0)	0 (0)	1 (1.4)	
	Uterus	0 (0)	0 (0)	1 (1.4)	
	missing	0	0	2	
Relapse before HSCT (after CART1, CART2, if any)	No relapse	19 (100)	21 (100)	1 (1.4)	Not done
	Molecular relapse			29 (40.3)	
	Relapse			42 (58.3)	

Characterization of the relapse before HSCT	No relapse	19 (100)	21 (100)	1 (1.4)	Not done
	Molecular relapse			29 (40.3)	
	Progression/Hematological Relapse			27 (37.5)	
	CNS +/- BM			8 (11.1)	
	EMD (no CNS) +/- BM			7 (9.7)	
Donor type (detailed)	Identical sibling	3 (15.8)	2 (9.5)	7 (9.9)	Not done
	Matched other relative	0 (0)	2 (9.5)	0 (0)	
	Mismatch relative 1 locus	0 (0)	1 (4.8)	0 (0)	
	Haploidentical HSCT	9 (47.4)	8 (38.1)	26 (36.6)	
	UD 10/10	4 (21.1)	4 (19)	21 (29.6)	
	UD 9/10	3 (15.8)	2 (9.5)	13 (18.3)	
	UD 8/10	0 (0)	0 (0)	1 (1.4)	
	UD (missing HLA)	0 (0)	0 (0)	2 (2.8)	
	UCB (missing HLA)	0 (0)	1 (4.8)	0 (0)	
	UCB 5/6	0 (0)	1 (4.8)	0 (0)	
	Double UCB	0 (0)	0 (0)	1 (1.4)	
	missing	0	0	1	
Source of cells	BM	3 (15.8)	6 (30)	20 (28.2)	0.15
	PB	16 (84.2)	12 (60)	50(70.4)	
	CB	0 (0)	2 (10)	0 (0)	
	Double CB	0 (0)	0 (0)	1 (1.4)	
	missing	0	1	1	

Table S4. Details and additional patients, disease and transplant characteristics of children and adults receiving HSCT after CAR19 T cell therapy. *Abbreviations: CART2: second CAR-T cell infusion; CB: cord blood; CML: chronic myeloid leukemia; CNS: central nervous system; CR: complete remission; EMD: extra-medullary disease; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; Mol: molecular; MRD: minimal residual disease; UD: unrelated donor.*

Variables	Modalities	Adult (N=38)	Child (N=74)	P value
HSCT planned before CAR-T	No	24 (66.7)	52 (71.2)	0.63
	Yes	12 (33.3)	21 (28.8)	
	missing	2	1	
Patient sex	Female	14 (36.8)	32 (43.2)	0.51
	Male	24 (63.2)	42 (56.8)	
Disease risk at diagnosis	standard	23 (65.7)	40 (69)	0.75
	high	12 (34.3)	18 (31)	
	missing	3	16	
Months from HSCT to relapse before CAR19 T cell therapy	No previous HSCT	18 (48.6)	48 (64.9)	0.34
	(0,6]	3 (8.1)	5 (6.8)	
	(6,12]	6 (16.2)	6 (8.1)	
	(12,48]	10 (27)	15 (20.3)	
	missing	1	0	
Reason of the HSCT (detailed)	High-risk cytogenetics/mutations (before CAR-T)	1 (2.6)	3 (4.1)	Not done
	High disease burden (before CAR-T)	2 (5.3)	9 (12.2)	
	Product out-of-specification	1 (2.6)	0 (0)	
	Standard of care	3 (7.9)	0 (0)	
	CAR-T Non permanent	1 (2.6)	0 (0)	
	CD19 Hematogones	0 (0)	1 (1.4)	
	CML clone	0 (0)	1 (1.4)	
	Loss of B-cell aplasia	3 (7.9)	14 (18.9)	
	Low/suboptimal CAR19 T cell expansion	1 (2.6)	0 (0)	
	MRD+ (after CAR-T)	6 (15.8)	23 (31.1)	
	Hematological relapse (after CAR-T)	19 (50)	23 (31.1)	
	HSCT for secondary malignancy (MDS) post CAR-T	1 (2.6)	0 (0)	
Age at this HSCT	median [IQR]	26 [22.5-37.9]	9.5 [7.2-13.6]	Not done
	(range)	(18.6-67.8)	(1.5-18)	
EMD at ALL diagnosis	No	27 (73)	63 (86.3)	Not done
	CNS	3 (8.1)	7 (9.6)	
	CNS+Facial nerve	0 (0)	1 (1.4)	
	CNS+Testis	0 (0)	1 (1.4)	

	CNS+Testis+Kidney+Bone+Nodes	1 (2.7)	0 (0)	
	Bone	3 (8.1)	1 (1.4)	
	Kidney	1 (2.7)	0 (0)	
	Lytic	1 (2.7)	0 (0)	
	Node	1 (2.7)	0 (0)	
	missing	1	1	
BCR-ABL	No	32 (84.2)	63 (90)	0.37
	Yes	6 (15.8)	7 (10)	
	missing	0	4	
MLL	No	33 (91.7)	62 (88.6)	0.75
	Yes	3 (8.3)	8 (11.4)	
	missing	2	4	
Number of HSCT before CAR-T	0	18 (47.4)	48 (64.9)	**0.04**
	1	18 (47.4)	26 (35.1)	
	2	2 (5.3)	0 (0)	
EMD at CAR-T apheresis	No	25 (73.5)	54 (73)	Not done
	CNS	2 (5.9)	13 (17.6)	
	CNS+Optic Nerve	0 (0)	3 (4.1)	
	CNS+Testis	0 (0)	1 (1.4)	
	Bone	3 (8.8)	0 (0)	
	Breast+Kidney+Bone	1 (2.9)	0 (0)	
	Cutaneous	0 (0)	2 (2.7)	
	Lytic	1 (2.9)	0 (0)	
	Node	1 (2.9)	0 (0)	
	Testis	0 (0)	1 (1.4)	
	Testis+Kidney+Bone	1 (2.9)	0 (0)	
	missing	4	0	
EMD at CAR-T lymphodepletion	No	26 (70.3)	69 (94.5)	Not done
	CNS	1 (2.7)	1 (1.4)	
	CNS+Cutaneous	0 (0)	1 (1.4)	
	CNS+Facial nerve	0 (0)	1 (1.4)	
	Bone	6 (16.2)	0 (0)	
	Breast+Pancreas+Nodes	1 (2.7)	0 (0)	
	Cutaneous	0 (0)	1 (1.4)	
	Lytic	1 (2.7)	0 (0)	
	Node	1 (2.7)	0 (0)	
	Uterus	1 (2.7)	0 (0)	
	missing	1	1	
CART2 between CART1 and this HSCT	No	33 (86.8)	62 (83.8)	0.67
	Yes	5 (13.2)	12 (16.2)	
B-cell aplasia	BCA loss	17 (51.5)	40 (54.1)	0.77
	BCA not reached	1 (3)	1 (1.4)	
	BCA ongoing	15 (45.5)	33 (44.6)	
	missing	5	0	

Characterisation of the relapse before HSCT	No relapse	13 (34.2)	28 (37.8)	0.23
	Molecular relapse	6 (15.8)	23 (31.1)	
	Progression/Hematological Relapse	12 (31.6)	15 (20.3)	
	CNS +/- BM	3 (7.9)	5 (6.8)	
	EMD (not CNS) +/- BM	4 (10.5)	3 (4.1)	
Donor type (detailed)	Identical sibling	4 (10.9)	8 (10.8)	Not done
	Matched other relative	0 (0)	2 (2.7)	
	Mismatched relative 1 locus	0 (0)	1 (1.4)	
	Haploidentical HSCT	7 (18.9)	36 (48.5)	
	UD 10/10	14 (37.8)	15 (20.2)	
	UD 9/10	9 (24.3)	9 (12.2)	
	UD 8/10	0	1 (1.4)	
	UD (HLA missing)	1 (2.7)	1 (1.4)	
	UCB 5/6	0 (0)	1 (1.4)	
	UCB (missing HLA)	1 (2.7)	0 (0)	
	Double UCB	1 (2.7)	0 (0)	
	missing	1	0	

Table S5. Outcome according to time between CAR-T infusion and HSCT (months).

		OS	**LFS**	**RI**	**NRM**
Months CAR-T to HSCT	[0-3]	75.6 [47.1-90.1]	60.6 [34.6-79]	33.8 [13.2-56]	5.6 [0.3-23.1]
	[3,6]	68.9 [50.7-81.4]	66.1 [48-79.2]	14 [5-27.5]	19.9 [8.6-34.6]
	[6,60]	64.6 [49-76.6]	43 [28.6-56.6]	45.3 [30.5-58.9]	11.8 [4.7-22.5]
	P value	0.8	0.16	**0.02**	0.27