haematologica
Journal of the Ferrata Storti Foundation

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Received: February 4, 2026.
Accepted: July 27, 2026.

Citation: Anna Ossami Saidy, Bettina Altmann, Pearl van Heteren, Matthias Stelljes, Georg Lenz, Julia Marx, Justin Hasenkamp, Friedrich Stölzel, Peter Dreger, Peter Lutz Müller, Inken Hilgendorf, Gerald G. Illerhaus, Guido Kobbe, Roland Schroers, Matthias Hänel, Stephan Fuhrmann, Katrin Linke, Carsta Köhler, German Ott, Norbert Schmitz, Marita Ziepert and Bertram Glass. Allogeneic stem cell transplantation after myeloablative conditioning with fludarabine, thiotepa, and cyclophosphamide in relapsed or refractory aggressive B-cell and T-cell lymphomas: results of the prospective ASTRAL study.
Haematologica. 2026 Aug 27. doi: 10.3324/haematol.2026.300658 [Epub ahead of print]

Allogeneic stem cell transplantation after myeloablative conditioning with fludarabine, thiotepa, and cyclophosphamide in relapsed or refractory aggressive B-cell and T-cell lymphomas: results of the prospective ASTRAL study

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Running Head
Allo SCT after MAC in relapsed aggressive lymphoma

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Authors' contributions
BG, NS, MZ, and BA conceptualised and designed the study. BG, NS, and GWT acquired funding. BG, PvH, AOS, SF and KL were responsible for methodology and project administration and supervised the project. Data collection was undertaken by MS, GL, JM, JH, FS, PD, LPM, IH, GI, GK, RSch and MH. BG, AOS, PvH, BA, and MZ accessed and verified the underlying data and were responsible for data interpretation. GO performed characterization of the lymphoma samples for reference pathology. BA and MZ performed statistical analyses and provided figures. AOS, BG, NS, BA, and PvH wrote, reviewed, and edited the original manuscript. All authors reviewed and

approved the final manuscript and had full access to all study data, sharing final responsibility for the decision to submit for publication.

Data-sharing statement

Anonymised, individual participant data that underlie the results reported in this article are available for sharing upon reasonable request. Researchers must submit a detailed research proposal specifying the intended use of the data for review and approval by an independent data access committee. Requests should be directed to the corresponding author within 24 months of publication.

Trial registration

The study is registered with ClinicalTrials.gov, number NCT04121507.

Acknowledgments

The authors thank the patients who participated in this study and their families. We also thank the research assistants at all participating centres and the data centre (IMISE/ZKS Leipzig), including Sigrid Haupt, Beate Mann, Katja Rillich, Madlen Dörschmann and Maren Ciuciu and Riemser Pharma GmbH for sponsoring.

Funding

This study received funding from Takeda Pharmaceutical. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Authors' Disclosures

AOS received honoraria and travel grants from Kite Gilead.

GL received research grants not related to this manuscript from AGIOS, AQUINOX, AstraZeneca, Bayer, Celgene, Gilead, Janssen, MorphoSys, Novartis, F. Hoffmann-La Roche Ltd, and Verastem.

G.L. received honoraria not related to this study from ADC Therapeutics, AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Constellation, Genase, Genmab, Gilead, Hexal/Sandoz, Immagene, Incyte, Janssen, Karyopharm, Lilly, Miltenyi, MorphoSys, MSD, NanoString, Novartis, PentixaPharm, Pierre Fabre, F. Hoffmann-La Roche Ltd, and Sobi.

MSt has served as a consultant for Pfizer, MSD, Bristol-Myers Squibb (BMS), Incyte, Takeda, Astellas, Autolus, Sanofi and Amgen; as a speaker for Pfizer, Medac, MSD, Astellas, Jazz Pharmaceuticals, Amgen, Novartis, Gilead, Celgene, BMS, AbbVie, and Incyte; has received research funding from Pfizer; and has received travel support from Medac, Sanofi and Pfizer.

NK received research grants from Neovii, JAZZ, BMS, Riemser, Novartis and honoraria from Neovii, Sanofi, JAZZ, BMS, Riemser, Kite Gilead, AOP Pharma, Amgen and Novartis.

NS received travel grants from Roche, Gilead, honoraria from Roche and research support from Janssen and Astra Zeneca. He owns stocks from BMS

PD received honoraria from Gilead Sciences, AbbVie, Bristol Myers Squibb/Celgene, Roche, BeiGene; reports a consulting or advisory role for Gilead Sciences, AbbVie, BeiGene, Bristol Myers Squibb/Celgene, Miltenyi Biomedicine; received research funding from RIEMSER and travel and accommodation support from BeiGene and Gilead Sciences.

LPM held an advisory role or expert testimony for Pfizer, Gilead, Novartis, Amgen and received honoraria and/or travel grants from AbbVie, Bristol-Myers Squibb, Gilead, Sanofi-Aventis as well as financing of scientific research from Amgen.

BG reports a consulting or advisory role for Roche Pharma AG, BMS GmbH & Co. K, Kite, a Gilead company, Novartis, RIEMSER, Jazz Pharmaceuticals, Miltenyi Biotec, Janssen, AbbVie and received research funding from Roche and RIEMSER.

Abstract

While allogeneic stem cell transplantation (alloSCT) remains the only curative option for patients with relapsed T-cell lymphoma, its place in the treatment algorithm of aggressive B-cell lymphoma is changing.

This multicentre, prospective, investigator-initiated trial investigated the efficacy and toxicity of a myeloablative conditioning regimen comprising fludarabine, thiotepa, and cyclophosphamide (FTC) prior to alloSCT in patients with relapsed/refractory (r/r) aggressive B-cell or T-cell lymphoma.

Among 60 patients, PFS at one and two years was 40% (95% CI 28-52) and 36% (95% CI 24-49), OS was 43% (95% CI 31-56) and 37% (95% CI 25-50), respectively, without significant differences between 42 patients with B-cell and 18 patients with T-cell lymphoma. The primary endpoint of the study defined as 1-year PFS of 50% was not met. The cumulative incidence of progression/relapse at two years was 34% (95% CI 19-49) for B- and 11% (95% CI 0-26) for T-cell patients. Cumulative incidence of NRM was 25% (95% CI 14-36) at day 100 and 35% (95% CI 23-47) at one year. Twelve patients who had failed CAR T-cell therapy (CART) had outcomes comparable to patients without prior CART.

In T-cell lymphoma, relapse after alloSCT was notably low, reflecting a strong graft-versus-lymphoma-effect. In B-cell lymphomas, our data suggest that alloSCT can be effective after CART failure, with more than one-third of patients being in remission after two years. These findings support the continued use of alloSCT in patients with aggressive lymphomas. Substantial NRM observed after FTC calls for the continued search of better tolerated conditioning regimens.

Introduction

Despite recent progress in first-line treatment of large B-cell lymphoma (LBCL), approximately 30% of all LBCL patients are either refractory or relapse after a short remission (r/r patients)[1]. Treatment with anti-CD19 chimeric antigen receptor T-cells (CART) has recently been established as the standard of care for such patients. However, with a three-year PFS-rate of 50·9% for lisocabtagene maraleucel (liso-cel) and a four-year PFS-rate of 41·8% for axicabtagene ciloleucel (axi-cel) and taking into consideration the significant toxicities reported after CART, results are far from optimal and further improvement is needed[2,3]. Although innovative therapies such as bispecific antibodies show promising early results also in patients failing CART, allogeneic stem cell transplantation (alloSCT) remains a valuable therapeutic option because it may cure a substantial proportion of patients with recurrent disease.

Patients with peripheral T-cell lymphomas (PTCL) face a dismal prognosis after failure of first-line therapy with alloSCT being the only curative option for such patients[4-6].

In a prospective, randomized, study, we previously reported outcomes after alloSCT in patients with LBCL and PTCL following myeloablative conditioning (MAC) with fludarabine, busulfan, and cyclophosphamide (FBC)[7]. Because of high non-relapse mortality (NRM) (35% at one year) seen in that study, particularly due to a notable incidence of veno-occlusive disease (VOD), we sought to improve NRM and overall survival (OS) by substituting busulfan with thiotepa, as thiotepa is not typically associated with VOD. Thiotepa is routinely administered prior to autologous and allogeneic transplantation, with low rates of NRM[8-10]. Furthermore, we wanted to describe the efficacy and safety of alloSCT in patients failing CART.

Materials and Methods

Additional information regarding the methods is provided in the supplement.

Eligibility criteria

ASTRAL (**A**llogeneic **S**tem cell **TR**ansplantation in **A**ggressive **L**ymphoma) was an open-label, nationwide, multicentre, prospective, investigator-initiated phase II study of the German Lymphoma Alliance (GLA). Patients aged ≥18 years with r/r aggressive B- or T-cell lymphoma according to the revised 2016 WHO criteria having a fully matched (10/10) related or unrelated donor, were included[11]. Imaging with CT or preferably PET-CT at last relapse and after two to three cycles of salvage therapy was mandatory. Patients who had failed autologous stem cell transplantation (autoSCT) or had achieved a partial response (PR) after two or three cycles of salvage treatment were included. Notably, we also included patients with stable (SD) or progressive disease (PD) as well as patients failing CART. Patients with early relapse (<12 months) achieving a complete response (CR) after two or three cycles of salvage treatment could also be included.

Procedures

The study was registered with the EU Clinical Trials Register in 2018 (EudraCT number: 2018-003668-30) and with ClinicalTrials.gov, number NCT04121507, it was approved by central and local ethics committees. All patients gave written informed consent before enrolment. The study was performed in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Patients received MAC with fludarabine 25 mg/m² (days -8 to -4), thiotepa 5 mg/kg (days -6 to -4), and cyclophosphamide 60 mg/kg (days -3 to -2) prior to alloSCT. GvHD prophylaxis was administered in accordance with individual center protocols. Reporting of adverse events grades ≥ 3 according to CTCAE version 4·03 and serious adverse events of any grade was obligatory until day 100 after alloSCT. Response assessment was performed according to Lugano criteria[12,13].

Outcomes

The primary endpoint progression free survival (PFS) at one year was defined as time from the first day of conditioning until one of the following events: progression, relapse, or death due to any cause, whichever came first. The incidence and severity of acute and chronic GvHD is reported as defined by Glucksberg et al.[14] and Filipovich et al.[15].

Statistical analysis

The aim of the trial was to determine the efficacy and toxicity of FTC conditioning followed by alloSCT. Sample size calculation used historical data from the CORAL trial, which reported a one-year PFS of 35% in a comparable autoSCT-treated cohort[16]. The protocol steering committee set a 50% PFS benchmark as clinically meaningful improvement for this trial. This target was based on the assumption that the FTC regimen would reduce toxicity and lower NRM compared to FBC[7]. A sample size of 70 patients ensured a robust Kaplan-Meier estimate for one-year PFS with a 95% confidence interval (CI) of ±12%, excluding a true one-year PFS below 38%.

For calculation of univariate and multivariate Cox regression models, please refer to the supplement. Subgroup analyses were of explorative nature. Significance level was set at p = 0.050. Statistical analyses were done with IBM SPSS Statistics 29.0, PASS 22.0.3, R V4.3.0, package cuminc and KM-Win V1.5.3.

Results

From June 2019 to December 2021, 61 patients were enrolled by 11 German transplantion centres. One patient had to be excluded because no stem cell donor was found. Forty-two patients were diagnosed with aggressive B-cell lymphoma, including 35 patients with LBCL and 7 patients with an aggressive course of mantle cell lymphoma, and 18 patients with PTCL (supplemental table 1). Median

age was 57 years (range 21 - 69), 72% of patients were male, 58% had elevated lactate dehydrogenase (LDH) levels and 52% had advanced disease stage at transplant. Nineteen and 28% of patients with B-cell and T-cell lymphoma had a high-intermediate to high IPI score at staging before FTC. Bulky disease (defined as ≥7·5 cm) was present in 21% of patients with B-cell lymphoma but in none of the patients with T-cell lymphoma. Thirty-one percent of patients with B-cell lymphoma and 67% of patients with T-cell lymphoma had previously failed autoSCT. Patients had received a median of three prior lines of therapy (range 1 – 6), including autoSCT in 42% of all patients and CART in 29% of the B-cell lymphoma patients. Across all study patients, 80% had a duration of last response of ≤12 months and 83% had measurable disease (no CR) prior to FTC. Twenty-two patients (37%) were refractory to the last line of therapy prior to ASTRAL study treatment. The median Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score was 1·5, with 38% displaying scores ≥ 3. Patient characteristics were similar for patients with B-cell and T-cell lymphoma and for patients with and without previous CART. A summary of patient characteristics at last staging before the start of conditioning is shown in table 1. A summary of the histological subtypes in patients with LBCL and PTCL is presented in supplemental table 1.

Twenty-two percent of patients had a matched sibling donor (MSD), while 78% received transplants from matched unrelated donors (MUD). The median number of infused CD34+-cells/kg bodyweight was 6·6 x 10^6 (range 2·3 – 15·6; IQR 5·2 – 8·6).

For GvHD prophylaxis, anti-thymocyte globulin, mycophenolate mofetil, cyclosporine A, tacrolimus and methotrexate were used in 87%, 90%, 65%, 37% and 7% of patients. Other prophylactic regimens were applied in 7% of cases. Neutrophil engraftment (ANC > 0·5 x 10^9/L) occurred at a median of 12 days (range 8 – 32), platelet recovery (> 20 x 10^9/L) at a median of 13 days (range 9 – 28), with 10 patients (17%) not recovering platelet counts > 20 x 10^9/L by day 50.

Most common and expected non-haematological grade ≥ 3 toxicities were infections, renal complications, mucositis, and GI toxicity. Noteworthy, CNS toxicity and cardiac arrhythmias occurred in 13% and 12% of patients, respectively. Five patients developed veno-occlusive disease (VOD) grade ≥ 3. A summary of all adverse events can be found in table 2 and supplemental table 2. The frequencies of acute (aGvHD) and of chronic graft-versus-host disease (cGvHD) of any grade, were 66% and 30%. Of patients with aGvHD, 46% experienced grades 3 – 4 (supplemental table 3).

The overall complete response (CR) rate was 52% (95% CI 38 - 65); 67% (95% CI 41 - 87) in patients with T-cell and 45% (95% CI 30 - 61) in patients with B-cell lymphoma; 42% of patients with previous CART and 47% of patients without prior CART achieved CR.

After a median observation time of 30 months (range 0·3-39·0, IQR 15 – 34) the PFS-rates at one and two years were 40% (95% CI 28 - 52) and 36% (95% CI 24 - 49), respectively (figure 1A). PFS rates at two years were 33% (95% CI 18 - 47) among patients with B-cell lymphoma and 44% (95% CI 21 - 67)

for patients with T-cell lymphoma (figure 2A). Two-year PFS for patients previously treated with CART was 40% (95% CI 11 - 69) compared to 30% (95% CI 14 - 46) for patients without previous CART (see figure 2A). Patients with mantle cell lymphoma had outcomes comparable to those of the remaining cohort (data not shown).

Notably, the primary endpoint, PFS at one year, which was hypothesized to be 50%, was not met.

Overall survival at one year was 43% (95% CI 31 - 56). At two years OS was 37% (95% CI 25 - 50) for all patients; 43% (95% CI 19 - 67) for patients with T-cell lymphoma, 35% (95% CI 20 - 50) for patients with B-cell lymphoma, 38% (95% CI 8 - 67) for those with prior CART and 33% (95% CI 16 - 50) for B-cell lymphoma patients without prior CART (see figure 1B and 2B). After censoring of four patients who died from COVID-19, the overall survival rate at two years for the complete cohort was 43% (95% CI 30 - 56).

The cumulative incidence rate of PD/relapse at one year was 25% (95% CI 14 - 36); 11% (95% CI 0 - 26) in patients with T-cell lymphoma, and 31% (95% CI 17 - 45) in patients with B-cell lymphoma, similar for patients with or without prior CART (see figure 1C and supplemental figure 1A).

At data cut-off, 37 patients (62%) had died, 27 patients with B-cell and 10 patients with T-cell lymphoma. Twelve patients (32%) died due to lymphoma. For the remaining 25 patients the causes of death were infections (35%) including 4 cases of COVID-19, GvHD (14%), respiratory failure (5%), renal insufficiency, liver toxicity, and CNS toxicity in one patient each; for two patients the cause of death was unknown (table 3). The four COVID-related deaths occurred between five and 19 months after alloSCT. Three of the respective patients died after experiencing progression/relapse, one died in complete remission six months after alloSCT.

Cumulative incidence of NRM at day 100 after FTC was 25% (95% CI 14 - 36), and 35% (95% CI 23 - 47) at one year for all patients (figure 1D and supplemental figure 1B) with no significant difference between patients with B- or T-cell lymphoma.

Univariate analysis showed impaired outcomes for patients with advanced stage disease (Ann Arbor III-IV) (HR 2·0 (95% CI 1·0 – 3·8) for PFS, p = 0·046; HR 2·2 (95% CI 1·1 - 4·4) for OS, p = 0·019) and for patients with ≥ 1 extra-lymphatic manifestation (HR 2·5 (95% CI 1·2 - 5·2) for PFS, p = 0·020; HR 2·6 (95% CI 1·2 - 5·6) for OS, p = 0·013). Patients with IPI 3-5 at time of transplant had significantly worse outcomes (HR 3·1 (95% CI 1·5 - 6·2) for PFS, p = 0·002; HR 3·5 (95% CI 1·7 - 7·2) for OS, p < 0·001). Patients being refractory to the last line of therapy prior to FTC showed a tendency for decreased survival without statistical significance (supplemental figure 2).

The very similar PFS and OS for B- and T-cell patients was confirmed by additional adjustment for prognostic factors in multivariate Cox regression analysis (IPI factors, sex, HCT-CI > 0, SD/PD prior to FTC) with a HR (B-cell vs. T-cell) of 1·1 (95% CI 0·5 - 2·4) for PFS and 1·0 (95% CI 0·4 – 2·2) for OS.

Discussion

With this prospective, nationwide study we aimed at improving the survival of patients with r/r aggressive B-cell and T-cell lymphoma by using a new MAC including fludarabine, cyclophosphamide in combination with thiotepa. The one-year PFS for the whole cohort was 40% (95% CI 28 - 52), thus failing to meet the primary endpoint. The early termination of patient recruitment – mainly because of the increasing use of CART in B-cell lymphoma patients – led to a limited number of 60 included patients (18 with T-cell lymphomas), with additional heterogeneity in B-cell histologies. Despite the lower number of recruited patients, the one-year PFS rate could be estimated with nearly the same precision as originally planned (CI ± 13%). Subgroup comparisons are to be considered exploratory. Despite this limitation, notable differences in outcomes emerged between T- and B-cell lymphomas. Among patients with T-cell lymphoma, the two-year PFS- and OS-rates were comparable to other retrospective and the prospective AATT study using MAC regimens[17,18]. In patients with aggressive B-cell lymphoma, the two-year PFS-rate was 33% and two-year OS was 35%. These survival rates likely reflect the effects of the conditioning regimen and the graft-versus-leukaemia (GvL) effect. Remarkably, more than one-third of B-cell lymphoma patients receiving alloSCT after CART failure, remained in remission at two years post-transplant. This ~~strongly~~ demonstrates general feasibility of alloSCT after CART failure and suggests that alloSCT has relevant efficacy in this setting. The median OS of selected patients able to receive further conventional therapy after CART failure has been reported as only 5·2 – 8·5 months[19]. In light of such data, a two-year OS of 38% for allografted patients previously treated with CART is ~~highly~~ encouraging, although cautious interpretation in light of the limited number of patients with CART-pretreatment is advisable. Similar results were reported in two multicenter retrospective analyses[20,21]. In support of the excellent anti-lymphoma effect of alloSCT, we and others recently reported rather low relapse rates after alloSCT, in contrast to high relapse incidences after CART, especially in high-risk patients[22,23]. In very high-risk patients with aggressive B-cell lymphoma a consolidative alloSCT following bridging therapy with CART may be considered.

In a previous randomised phase II study using fludarabine and cyclophosphamide in combination with busulfan (FBC) prior to alloSCT we observed one-year PFS- and OS-rates of 45% and 52%, respectively, for patients with B-cell lymphoma[7]. The results achieved with the FTC regimen replacing busulfan with thiotepa did not improve outcomes. Given that the primary endpoint was not achieved, the study must be considered negative. The reasons for the study's negative outcome are most likely multifactorial. Our hypothesis that changing myeloablative conditioning from FBC to FTC would reduce NRM was not confirmed. NRM remained as high as 35% at one year and thereby seems comparable to NRM observed after the FBC regimen in B- and T-cell lymphoma[4,7]. While the incidence of hepatic toxicity and veno-occlusive disease appeared slightly lower after FTC compared to FBC, other toxicities prevailed. In particular, an unexpectedly high number of patients experienced CNS toxicity, including

one fatal case. CNS toxicity may have been caused by thiotepa used at a relatively high total dose of 15 mg/kg. Thiotepa is well known to cross the blood-brain barrier and hence is frequently used as part of the preparatory regimen prior to autoSCT in patients with primary and secondary CNS lymphoma[8,9,24]. As other studies using thiotepa prior to autoSCT at lower doses (10 mg/kg) did not show excessive CNS toxicity, we assume that the dose of thiotepa used with the FTC regimen and/or the combination with fludarabine and cyclophosphamide ~~might have~~ led to enhanced neurotoxicity[8-10]. Alternatively, drugs used to prevent GvHD or infections after alloSCT might have interfered with the metabolism of thiotepa thereby causing excess toxicity. The protocol recommended ATG, CSA or tacrolimus, and short-course MTX or MMF for GvHD prophylaxis, allowing centers to follow their individual standard protocols. In practice, the most frequently used prophylaxis regimens combined ATG and MMF with a calcineurin inhibitor, reflecting the prevailing German standard at the time of the trial. Several studies have shown that ATG is safe and effective for GvHD prevention and that MMF offers comparable efficacy to MTX with a reduced risk of mucosal toxicity[25-29]. Therefore, the regimens used should generally be suitable to limit development of extensive GvHD and, consequently, NRM. However, as detailed information – such as immunosuppressant dosing – is not available, it cannot be definitively ruled out that the treatments may have contributed to the high NRM in some cases.
Overall, with respect to the increased CNS toxicity and the high NRM, the use of the FTC regimen has to be discouraged. Recently published data on alloSCT in aggressive B- and T-cell lymphomas report NRM rates less than 25% in recent years[30,31]. While these studies are retrospective and may therefore be subject to patient selection bias, the substantially lower NRM observed in these cohorts further supports the hypothesis that the FTC regimen is associated with significant toxicity and elevated NRM. Given the consistently high NRM following MAC – observed not only in our current cohort of heavily pretreated patients with aggressive lymphoma as well as in our previous cohort treated with the FBC regimen, but also in another study using a distinct MAC regimen[32] – reduced-intensity conditioning (RIC) may represent a promising alternative. As the effects of alloSCT in large parts are related to the GvL effect exerted by donor T-cells, RIC – while preserving the anti-lymphoma effect of alloSCT – may help to control NRM and improve survival. Retrospective analyses by EBMT and CIBMTR on alloSCT in patients with r/r LBCL showed a lower NRM in patients who received RIC compared to MAC protocols[33, 34]. Lower NRM was also seen in a prospective trial using RIC for patients with r/r lymphoma[35]. In T-cell lymphoma various studies reported lower NRM after alloSCT following RIC[36, 37]. Alternative approaches including reduced-dose TBI or radioimmunotherapy warrant further investigation[37-39].

This prospective study has limitations. In particular, the relatively low patient numbers result in rather wide confidence intervals for most outcome data presented. Furthermore, this was not a randomized study directly comparing the FTC regimen to FBC or other conditioning. Nonetheless, outcome data

are very similar to previous results of alloSCT in B- and T-cell lymphoma patients which we and others reported, increasing the plausibility of the data shown and the interpretations offered.

Overall, this study demonstrates that, despite a high overall mortality rate of 62%, alloSCT retains curative potential in aggressive B-cell and T-cell lymphomas. However, the problematic toxicity profile of MAC in general and FTC in particular remains a significant concern. In T-cell lymphoma, alloSCT remains the only curative option for patients failing first-line therapy. Exploratory analyses on B-cell lymphoma patients with prior exposure to CART did not reveal adverse outcomes after alloSCT in this specific cohort, supporting consideration of alloSCT as a potentially curative salvage option after CART failure in suitable patients.

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Tables

Table 1: Patient Characteristics

At last staging before transplantation	B-NHL (n=42)	B-NHL, no prior CART (n=30)	B-NHL, prior CART (n=12)	T-NHL (n=18)	Total (n=60)
Male Female	30 (71%) 12 (29%)	22 (73%) 8 (27%)	8 (67%) 4 (33%)	13 (72%) 5 (28%)	43 (72%) 17 (28%)
Age, median (range) Age > 60	57.5 (21, 69) 13 (31%)	57.5 (21, 69) 8 (27%)	58 (38, 67) 5 (42%)	56.5 (36, 68) 6 (33%)	57 (21, 69) 19 (32%)
LDH > Normal	24 (57%)	17 (57%)	7 (58%)	11 (61%)	35 (58%)
ECOG > 1	6 (14%)	4 (13%)	2 (17%)	0 (0%)	6 (10%)
Ann Arbor Stage III/ IV	19 (45%)	16 (53%)	3 (25%)	12 (67%)	31 (52%)
Extra-lymphatic involvement > 1	7 (17%)	6 (20%)	1 (8%)	3 (17%)	10 (17%)
IPI 3-5	8 (19%)	7 (23%)	1 (8%)	5 (28%)	13 (22%)
Bulk (≥ 7.5 cm)	9 (21%)	7 (23%)	2 (17%)	0 (0%)	9 (15%)
HCT-CI score, median (range) HCT-CI score > 0	1.5 (0, 7) 29 (69%)	2 (0, 7) 22 (73%)	1 (0, 4) 7 (58%)	1.5 (0, 6) 11 (61%)	1.5 (0, 7) 40 (67%)
Failure type* Primary refractory disease 1st relapse 2nd relapse 3rd or higher relapse	 19 (36%) 16 (39%) 3 (7%) 3 (7%)	 12 (41%) 14 (48%) 2 (7%) 1 (3%)	 7 (58%) 2 (17%) 1 (8%) 2 (17%)	 4 (22%) 9 (50%) 4 (22%) 1 (6%)	 23 (39%) 25 (42%) 7 (12%) 4 (7%)
Duration of last response* ≤ 12 months > 12 months	 34 (83%) 7 (17%)	 22 (76%) 7 (24%)	 12 (100%) 0 (0%)	 13 (72%) 5 (28%)	 47 (80%) 12 (20%)
No of lines prior to FTC, median (range)	3 (1, 6)	2 (1, 6)	4.5 (3, 5)	3 (2, 6)	3 (1, 6)
Prior failed autoSCT	13 (31%)	10 (33%)	3 (25%)	12 (67%)	25 (42%)
Prior CART	12 (29%)	--	12 (100%)	--	--
Disease status prior to FTC					

CR	8 (19%)	6 (20%)	2 (17%)	2 (11%)	10 (17%)
PR	19 (45%)	14 (47%)	5 (42%)	9 (50%)	28 (47%)
SD	7 (17%)	5 (17%)	2 (17%)	3 (17%)	10 (17%)
PD	8 (19%)	5 (17%)	3 (25%)	4 (22%)	12 (20%)

* one patient with B-NHL (no prior CAR T) without failure

NHL, Non-Hodgkin Lymphoma; FTC, myeloablative conditioning therapy with Fludarabin, Thiotepa, and Cyclophosphamide; ECOG, Eastern Cooperative Oncology Group performance-status score; LDH, lactate dehydrogenase; IPI, International Prognostic Index; HCT-CI, Hematopoietic Cell Transplantation-specific Comorbidity Index; autoSCT, autologous stem cell transplantation; CART, chimeric antigen receptor T-cell therapy; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease

Table 2: Non-haematological adverse events grade 3-5 according to CTCAE version 4.03 occuring in ≥ 10% of patients, reported until week 14 after FTC.

Adverse event	**n (%) of patients with grade 3-5**
Infection	40 (67%)
Renal	17 (28%)
Mucositis oral	14 (23%)
Diarrhea	8 (13%)
CNS toxicity	8 (13%)
Decreased appetite	7 (12%)
Cardiac arrhythmia	7 (12%)
Nausea	6 (10%)
Allergic reaction/ hypersensitivity	6 (10%)
Multiple organ dysfunction syndrome	6 (10%)
Respiratory failure	6 (10%)

GvHD as an adverse event is not included in this table. CNS, central nervous system; FTC, conditioning therapy with fludarabin, thiotepa and cyclophosphamide

Table 3: Treatment responses and survival data

Treatment response, n=60	**n (%); (95% CI)**
CR	31 (52%); (38%; 65%)
PR	1 (2%); (0%; 9%)
Primary progression	13 (22%); (12%; 34%)
Early NRM (prior to response assessment)	14 (23%); (13%; 36%)
Relapse after CR	2/31 (6%); (1%; 21%)
Survival rates (95% CI)	
PFS at 1 year	40% (28%; 52%)
OS at 1 year	43% (31%; 56%)
PFS at 2 years	36% (24%; 49%)
OS at 2 years	37% (25%; 50%)
Cumulative incidence rate of PD/Relapse (95% CI)	
PD/relapse rate at 100 days	17% (7%; 26%)
PD/relapse rate at 1 year	25% (14%; 36%)
PD/relapse rate at 2 years	27% (16%; 39%)
Cumulative incidence rate of NRM (95% CI)	
NRM rate at 100 days	25% (14%; 36%)
NRM rate at 1 year	35% (23%; 47%)
NRM rate at 2 years	37% (24%; 49%)
Cause of death n (%)	**37 (62%)**
Lymphoma-associated death	12/37 (32%)
Infection COVID 19 GvHD Respiratory failure Renal insufficiency Liver toxicity CNS toxicity Unknown	13/37 (35%) 4/37 (11%) 5/37 (14%) 2/37 (5%) 1/37 (3%) 1/37 (3%) 1/37 (3%) 2/37 (5%)

CI, confidence interval; CR, complete remission; PR, partial remission; PFS, progression-free survival; OS, overall survival; PD, progressive disease; NRM, non-relapse mortality; FTC, myeloablative conditioning therapy with fludarabin, thiotepa and cyclophosphamide

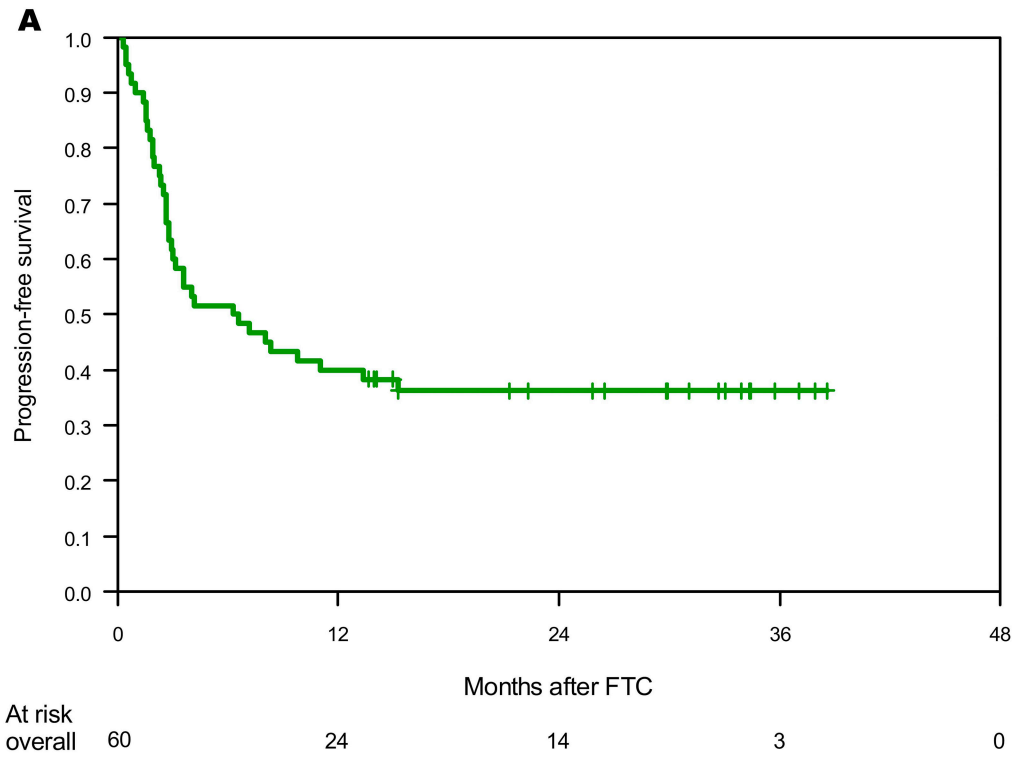
Figure Legends

Figure 1: Outcomes of all patients (n=60) irrespective of histology or treatment prior to FTC and alloSCT

A Progression-free survival; B Overall survival; C Cumulative incidence of progression/relapse; D Cumulative incidence of non-relapse mortality. FTC, conditioning therapy with fludarabin, thiotepa and cyclophosphamide; alloSCT, allogeneic stem cell transplantation

Figure 2: PFS, OS, RI and NRM of patients with aggressive T-cell and B-cell lymphoma: Separate survival curves for patients with T-cell lymphoma (red), with aggressive B-cell lymphoma without prior CAR T-cell treatment (dark blue) and for patients with aggressive B-cell lymphoma with prior CAR T failure (light blue).

A Progression-free survival; B Overall Survival; C cumulative incidence of progression/relapse (RI); D cumulative incidence of non-relapse mortality (NRM)
FTC, fludarabine, thiotepa and cyclophosphamide; alloSCT, allogeneic stem cell transplantation; PFS, progression-free survival; OS, overall survival; RI, relapse incidence; NRM, non-relapse mortality; w CART, with prior CAR T-cell therapy; wo CART, without prior CAR T-cell therapy


A
Progression-free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
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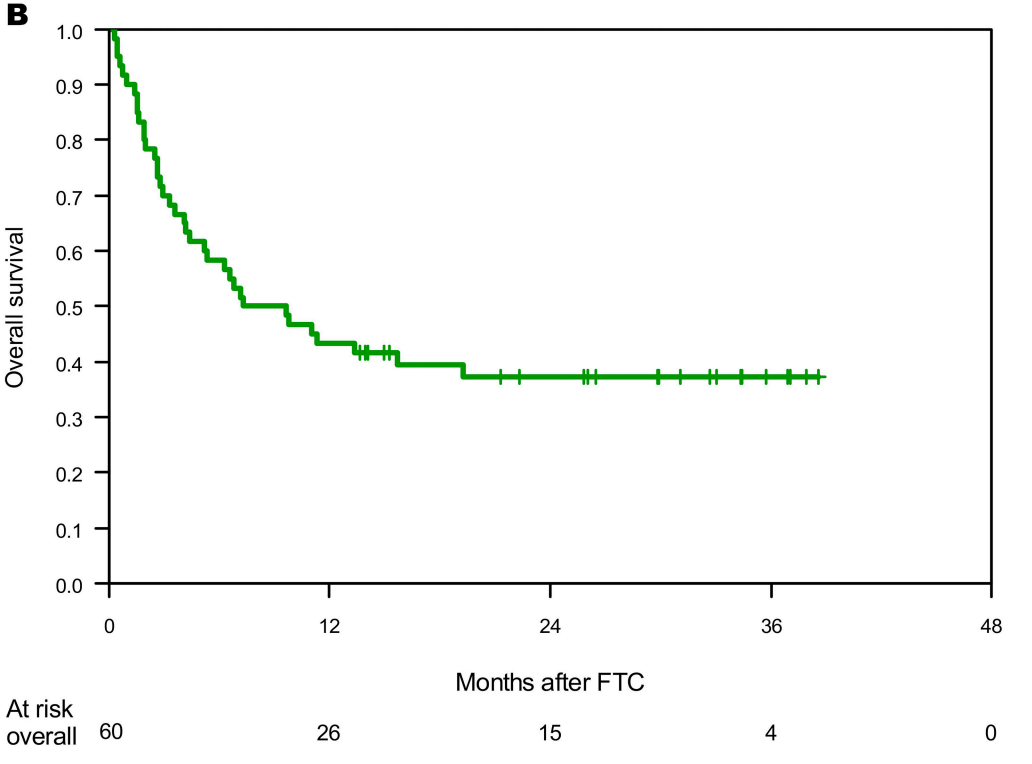
0.2
0.1
0.0
0
12
24
36
48
Months after FTC
At risk
overall 60 24 14 3 0


B
Overall survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
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12
24
36
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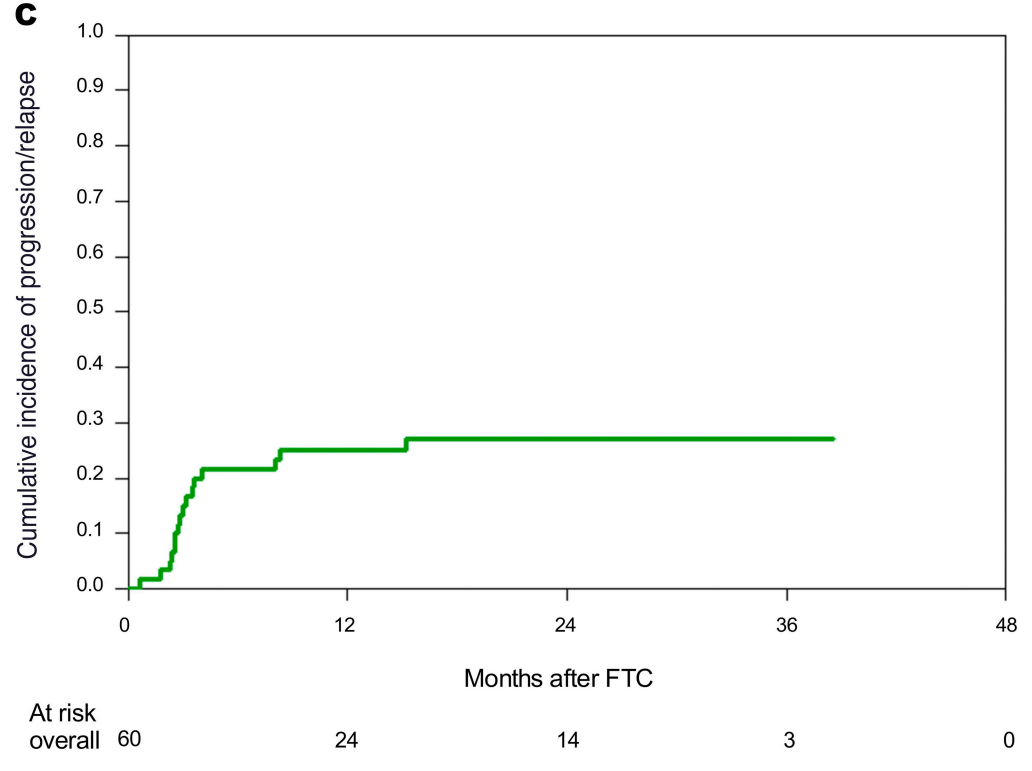
Months after FTC
At risk
overall 60 26 15 4 0


C
Cumulative incidence of progression/relapse
1.0
0.9
0.8
0.7
0.6
0.5
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12
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36
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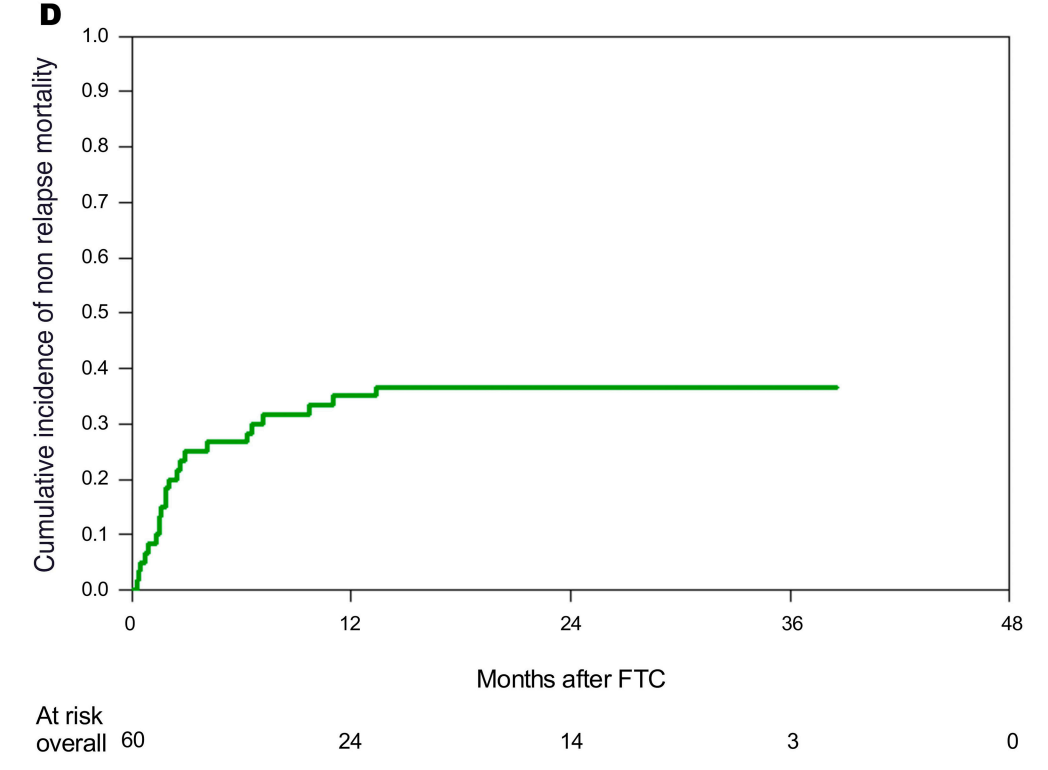
Months after FTC
At risk
overall 60 24 14 3 0


D
Cumulative incidence of non relapse mortality
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
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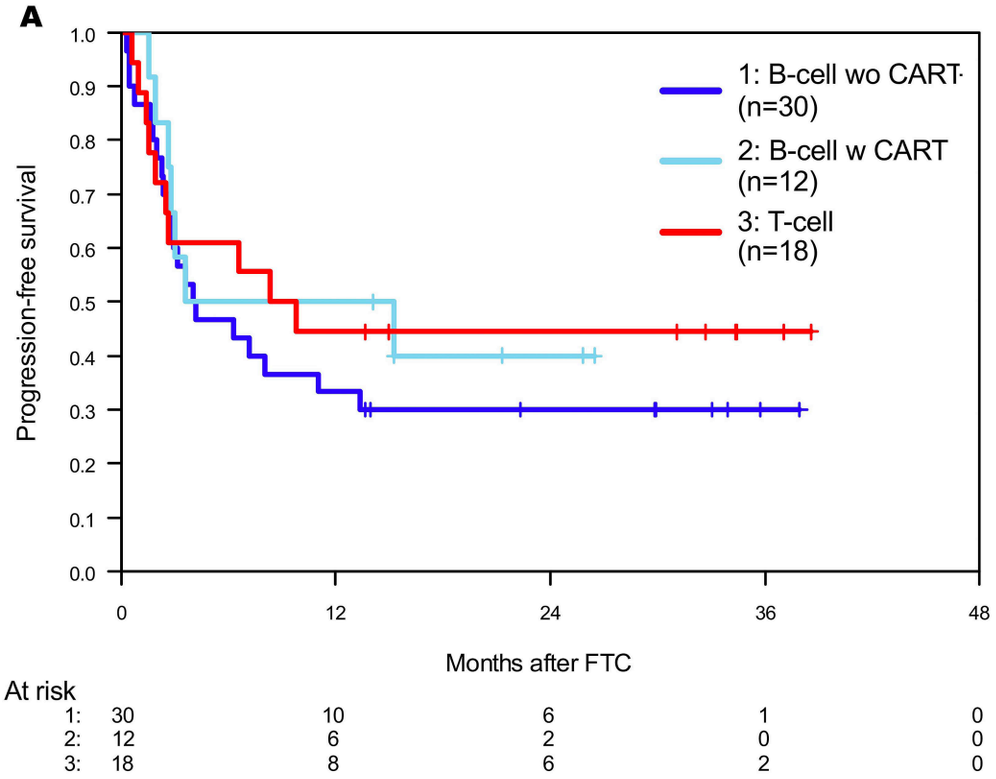
0.0
0
12
24
36
48
Months after FTC
At risk
overall 60 24 14 3 0


A
Progression-free survival
1.0
0.9
0.8
0.7
0.6
0.5
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0.3
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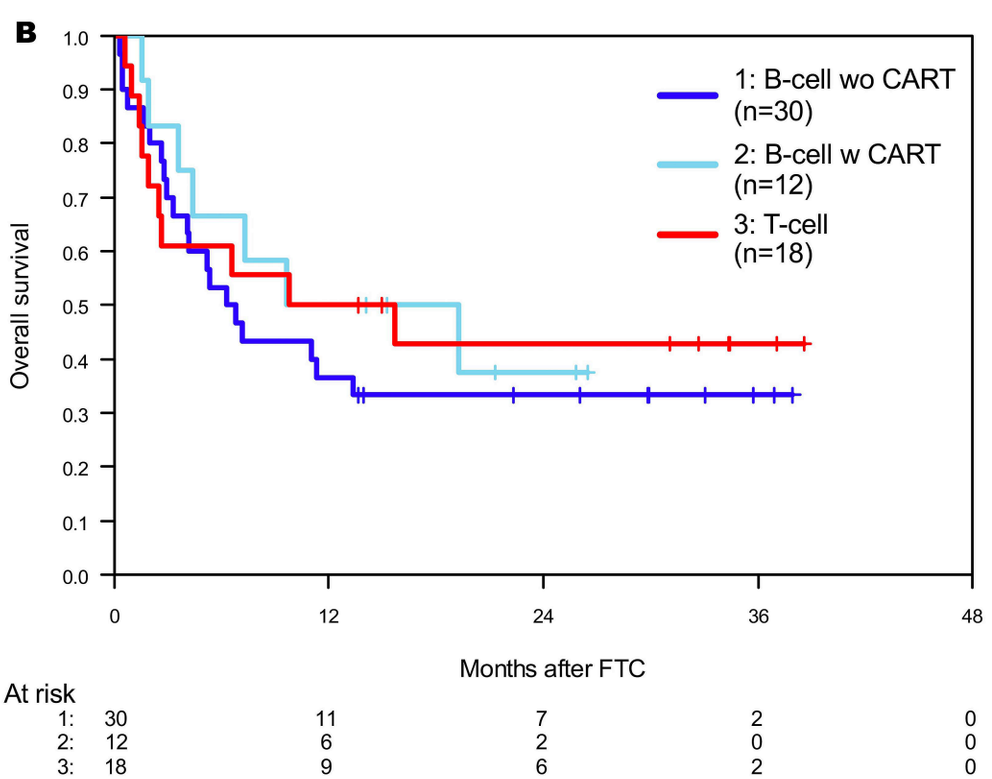
12
24
36
48
Months after FTC
1: B-cell wo CART (n=30)
2: B-cell w CART (n=12)
3: T-cell (n=18)
At risk
1: 30 10 6 1 0
2: 12 6 2 0 0
3: 18 8 6 2 0


B
Overall survival
1.0
0.9
0.8
0.7
0.6
0.5
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12
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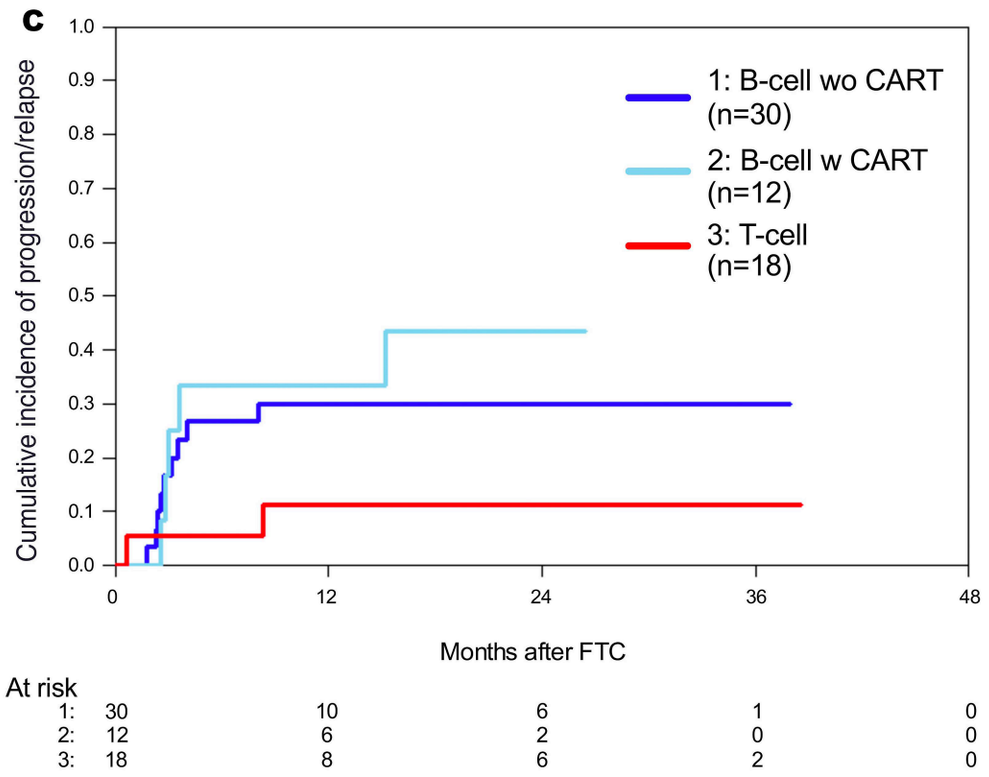
Months after FTC
1: B-cell wo CART (n=30)
2: B-cell w CART (n=12)
3: T-cell (n=18)
At risk
1: 30 11 7 2 0
2: 12 6 2 0 0
3: 18 9 6 2 0


C
Cumulative incidence of progression/relapse
1.0
0.9
0.8
0.7
0.6
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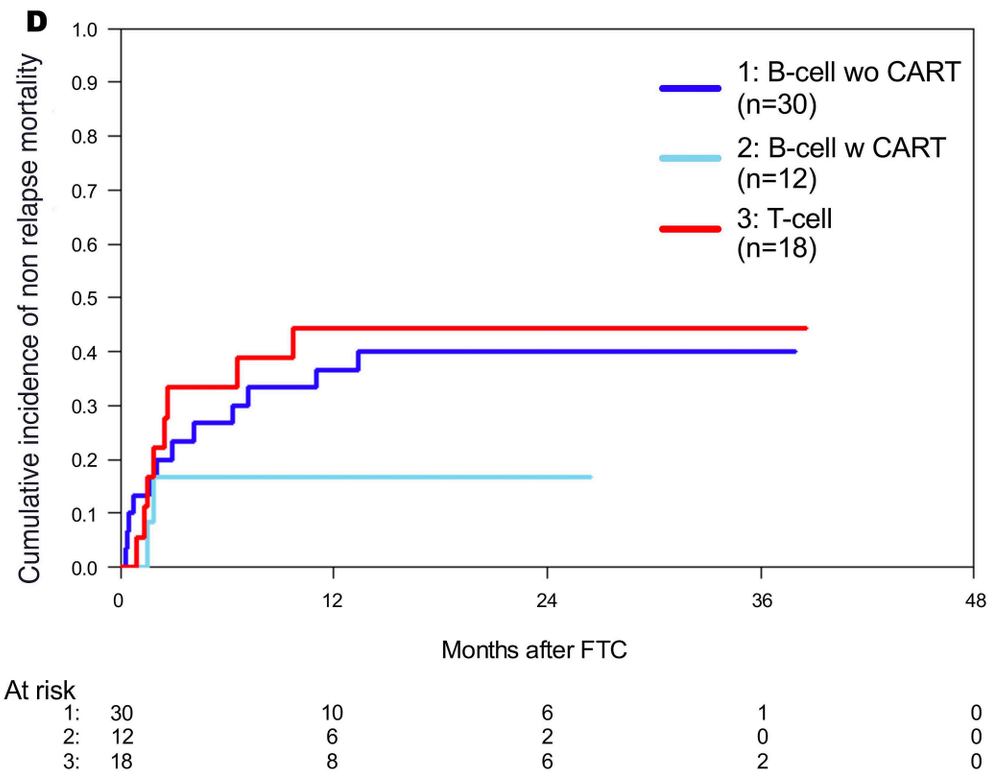
12
24
36
48
Months after FTC
1: B-cell wo CART (n=30)
2: B-cell w CART (n=12)
3: T-cell (n=18)
At risk
1: 30 10 6 1 0
2: 12 6 2 0 0
3: 18 8 6 2 0


D
Cumulative incidence of non relapse mortality
1.0
0.9
0.8
0.7
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0.0
0
12
24
36
48
Months after FTC
1: B-cell wo CART (n=30)
2: B-cell w CART (n=12)
3: T-cell (n=18)
At risk
1: 30 10 6 1 0
2: 12 6 2 0 0
3: 18 8 6 2 0

ASTRAL study - Supplemental Material

Supplemental Information on Methodology

Eligibility Criteria

The diagnosis of aggressive B- or T-cell lymphoma according to the revised 2016 WHO criteria was confirmed by an expert panel of haematopathologists at least once throughout the disease course. In addition to the described criteria in the manuscript, patients with an ECOG performance score of 0-3 and no severe organ dysfunctions were eligible. Major exclusion criteria were CNS involvement, active infection before transplantation, as well as HIV positivity.

Procedures

Imaging with CT or preferably PET-CT at last relapse and after two to three cycles of salvage therapy was mandatory according to protocol. Response assessment was performed according to Lugano criteria. Patients received myeloablative conditioning with fludarabine 25 mg/m² (days -8 to -4), thiotepa 5 mg/kg (days -6 to -4), and cyclophosphamide 60 mg/kg (days -3 to -2) (FTC) prior to alloSCT (see supplemental table 2). All cytotoxic agents were administered intravenously over two hours once per day. The study protocol recommended rabbit anti-thymocyte globulin (ATG), ciclosporine A (CSA) or tacrolimus, and short-course methotrexate (MTX) or mycophenolate mofetil (MMF) for GvHD prophylaxis. Effectively, GvHD prophylaxis was administered in accordance with individual center protocols. Procedures related to harvesting and transplantation of allogeneic stem cells were not part of the study treatment and were performed according to standards of participating centers.

Any adverse events (AE)s occurring after day 100 had to be reported if possibly related to the study medication. Severe infections (grade ≥ 4) and GvHD had to be documented until the end of the study. Restaging by PET-CT or CT scan was scheduled for week ten after alloSCT and at any time in case of clinically suspected relapse or progression.

Statistical Analysis

The aim of the trial was to determine the efficacy and toxicity of FTC conditioning followed by alloSCT. For sample size calculation, we used historical data from the CORAL trial, which reported a one-year PFS of 35% in a comparable cohort treated with autoSCT. The protocol steering committee defined a clinically meaningful improvement to 50% PFS as the benchmark for this trial. This target was based on the assumption that the FTC regimen would reduce toxicity and

lower NRM compared to the FBC regimen. The planned sample size of 70 patients was designed to establish a robust Kaplan-Meier estimate for one-year PFS with a 95% confidence interval (CI) of ±12%, thereby allowing exclusion of a true one-year PFS below 38%.

The study was closed prematurely after 60 patients had been included. Reasons for early termination of the trial was poor patient accrual and the fact that with sixty patients enrolled the one-year PFS rate could be estimated with nearly the same precision as originally planned (CI ± 13%).

Patient characteristics were analysed by $\chi 2$ test and, if necessary, by Fisher exact test. Response and relapse rates are presented with 95% CI (Clopper-Pearson).

Kaplan-Meier estimates at one and two years with 95% confidence intervals (CI) were calculated for PFS and OS.

Univariate Cox regression models were calculated for known prognostic factors: IPI factors (age > 60 years, LDH > N, ECOG > 1, stage III/IV, more than one extralymphatic lesion) and IPI score (0-2 vs. 3-5), reference pathology, prior CART, sex, type of treatment failure (SD/PD or relapse), duration of last response, response after salvage treatment, and HCT score were calculated.

For the multivariate Cox regression model comparing B- and T-cell regarding PFS and OS, we used the established five IPI factors an in addition, we adjusted for the factors with p-value < 0.1 in the univariate analysis (sex, HCT-CI > 0, SD/PD prior to FTC).

For the Cox regression models the estimates of are reported as hazard ratios with 95% CI and a corresponding p-value.

Cumulative incidence curves for time to progression/relapse (death without progression/relapse is counted as competing event) and for NRM (progression/relapse is counted as competing event) are presented and rates at day 100, at one and two years, with 95% CIs were calculated[1].

Subgroup analyses comparing T- and B-cell histology or CAR T-pretreated vs CAR T-naïve patients were performed.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Supplemental Table 1: Entities by reference (or local) pathology

Pathology	**Total (n=60)**
B-NHL	**42 (70%)**

DLBCL, not otherwise specified (NOS)	27 (64%)
T-cell/histiocyte-rich large B-cell lymphoma	1 (2%)
EBV-positive DLBCL, NOS	1 (2%)
Primary mediastinal (thymic) large B-cell lymphoma	1 (2%)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	4 (10%)
High-grade B-cell lymphoma, NOS	1 (2%)
Mantle cell lymphoma	7 (17%)
T-NHL	**18 (30%)**
Aggressive natural killer cell leukemia	1 (6%)
Enteropathy-associated T-cell lymphoma	1 (6%)
Peripheral T-cell lymphoma, NOS	5 (28%)
Angioimmunoblastic T-cell lymphoma	7 (39%)
Anaplastic large cell lymphoma, ALK-positive	1 (6%)
Anaplastic large cell lymphoma, ALK-negative	2 (11%)
Peripheral T-cell lymphoma with TFH phenotype	1 (6%)

NHL, Non-Hodgkin Lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, epstein-barr virus; TFH, T follicular-helper

Supplemental Table 2: Treatment schedule - Conditioning regimen FTC

Drug	Single dose	Total no. of single doses	Days	Doses / day	Application [a)]
Fludarabine	25 mg/m²	5	d -8 to -4	1	i.v. 2 h
Thiotepa	5 mg/kg	3	d -6 to -4	1	i.v. 2 h
Cyclophosphamide	60 mg/kg	2	d -3 to -2	1	i.v. 2 h

a) All infusion times are recommendations and may be modified.

Per study protocol, dose/route and treatment schedule were to follow the pertinent treatment guidelines and the respective local Summary of Product Characteristics (SmPCs).

Supplemental Table 3: Non-haematological adverse events grade 3-5 occuring in < 10% of patients until week 14 after FTC, GvHD not included

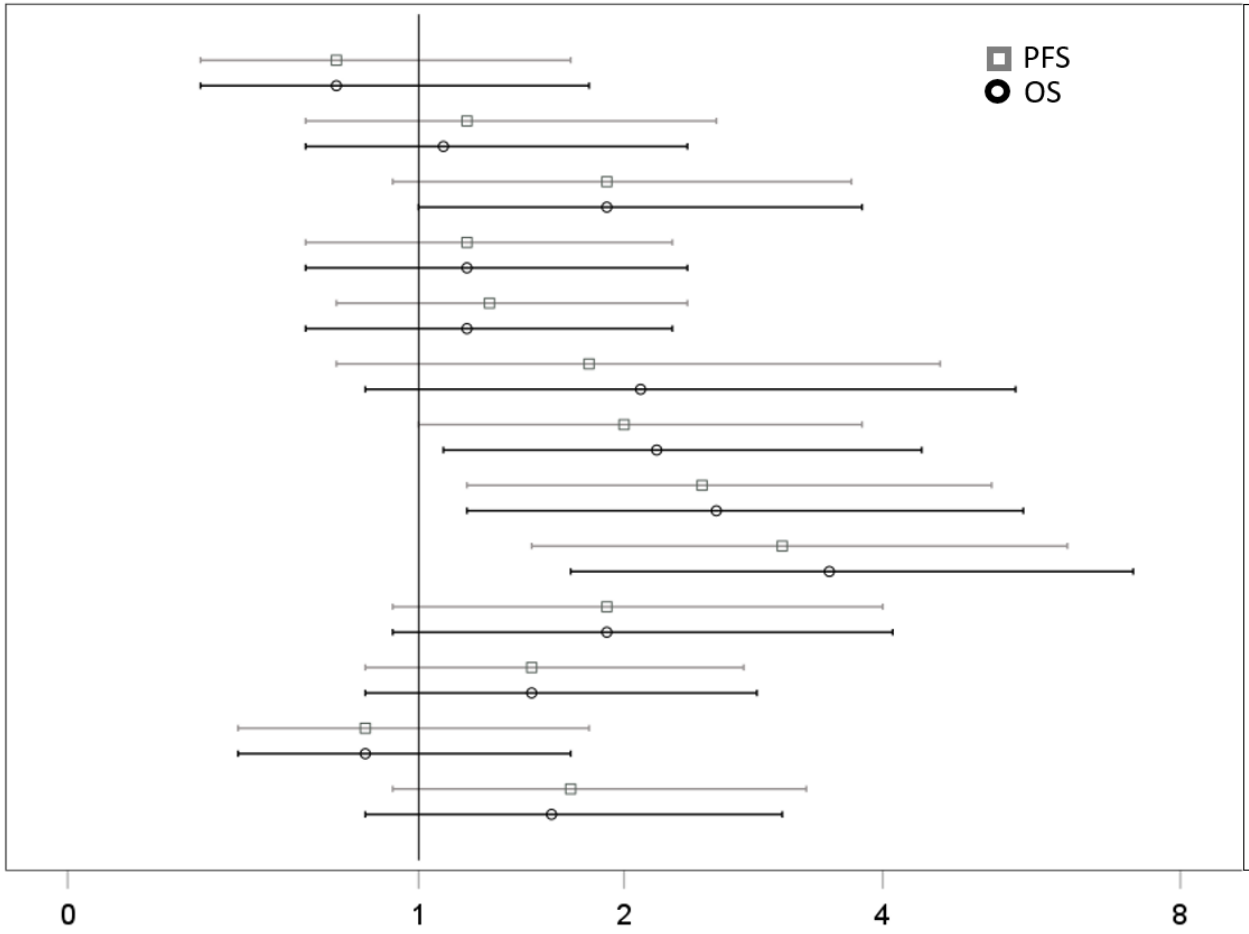
Adverse event	**n (%) of patients with grade 3-5**
Cardiac general	5 (8%)
Veno occlusive disease	5 (8%)
Hemorrhage/ bleeding	4 (7%)
Other liver toxicity	4 (7%)
Skin toxicity	3 (5%)
Vomitting	2 (3%)
Ileaus paralytic	2 (3%)
Back pain	2 (3%)
Syncope	2 (3%)
Peripheral neutropathy	1 (2%)
Thrombotic thrombocytopenic purpura	1 (2%)
Periorbital oedema	1 (2%)
Guillain-Barre syndrome	1 (2%)
Loss of consciousness	1 (2%)
Confusional state	1 (2%)
Bladder tamponade	1 (2%)
Haematuria	1 (2%)
Acute respiratory failure	1 (2%)
Hypercapnia	1 (2%)
Hyperglycaemia	1 (2%)
Pleural effusion	1 (2%)
Pulmonary hypertension	1 (2%)
Pulmonary oedema	1 (2%)
Hypertension	1 (2%)
Hypotension	1 (2%)

Supplemental Table 4: Acute and Chronic Graft-versus-Host Disease

Graft-versus-Host Disease	Number of patients (%)
Acute GvHD (patients alive on day 8 after transplantation: n = 57)	
missing	4/57 (7%)
no	18/57 (32%); 18/53 (34%)
yes	35/57 (61%); 35/53 (66%)
Maximum overall grade of acute GvHD	
1	4/35 (11%)
2	15/35 (43%)
3	10/35 (29%)
4	6/35 (17%)
Chronic GvHD (patients alive on day 101 after transplantation: n = 40)	
no	28/40 (70%)
yes	12/40 (30%)

GvHD, Graft-versus-Host Disease

Supplemental Figure 1: Forrest plot for univariate Cox regression models for progression-free and overall survival



Factor	HR [95% CI]	p-value
Prior CAR T-cell*	0.7 [0.3; 1.7]	0.479
	0.7 [0.3; 1.8]	0.495
B-cell vs. T-cell	1.2 [0.6; 2.6]	0.553
	1.1 [0.6; 2.4]	0.713
Female sex	1.9 [0.9; 3.7]	0.074
	1.9 [1.0; 3.8]	0.062
Age > 60 years	1.2 [0.6; 2.3]	0.633
	1.2 [0.6; 2.4]	0.531
LDH > Normal	1.3 [0.7; 2.4]	0.466
	1.2 [0.6; 2.3]	0.560
ECOG > 1	1.8 [0.7; 4.6]	0.223
	2.1 [0.8; 5.5]	0.121
Stage III/IV	2.0 [1.0; 3.8]	0.046
	2.2 [1.1; 4.4]	0.019
> 1 Extranodal involvement	2.5 [1.2; 5.2]	0.020
	2.6 [1.2; 5.6]	0.013
IPI 3 – 5	3.1 [1.5; 6.2]	0.002
	3.5 [1.7; 7.2]	< 0.001
HCT-CI > 0	1.9 [0.9; 4.0]	0.093
	1.9 [0.9; 4.1]	0.092
Failure type SD/PD	1.5 [0.8; 2.8]	0.249
	1.5 [0.8; 2.9]	0.222
Last response ≤ 12 months	0.8 [0.4; 1.8]	0.673
	0.8 [0.4; 1.7]	0.539
SD/PD before FTC	1.7 [0.9; 3.3]	0.090
	1.6 [0.8; 3.1]	0.154

* for B-NHL patients only. PFS, progression-free survival; OS, overall survival; CAR T-cell, chimeric antigen receptor t-cell therapy; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group performance status; IPI International Prognostic Index, HCT-CI, Hematopoietic Cell Transplantation (HCT)-specific Comorbidity Index; SD, stable disease; PD, progressive disease; FTC, fludarabin, thiotepa and cyclophosphamide

Reference

1. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496-509.