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Norbert Schmitz, Lorenz Truemper, Krimo Bouabdallah, Marita Ziepert, Mathieu Leclerc, et al.. A randomized phase 3 trial of auto vs. allo transplantation as part of first-line therapy in poor-risk peripheral T-NHL. *Blood*, 2021, 2020008825, 10.1182/blood.2020008825 . hal-03163608

**HAL Id: hal-03163608**

**<https://hal.umontpellier.fr/hal-03163608v1>**

Submitted on 31 Mar 2021

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**Titel: A randomized phase 3 trial of auto vs. allo transplantation as part of first-line therapy in poor-risk peripheral T-NHL**

**Running Head: Autologous vs. allogeneic transplantation in first-line T-NHL**

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**Key Points:**

- Conventional therapy consolidated by autoSCT remains a promising option to treat T-cell lymphoma patients.
- Relapsing or refractory patients with peripheral T cell lymphoma should be offered alloSCT.

**Prior presentations:**

The study was presented orally at the ASCO annual meeting 2019 (abstract 7503) and at the International Conference of Malignant Lymphoma (ICML Lugano) 2019 (abstract 058).

**Funding:**

Grants: Norbert Schmitz and Lorenz Truemper: Bundesministerium für Bildung und Forschung (BMBF, FKZ 01KG0705),

Olivier Tournilhac: Ministère de la Santé et des Solidarités (PHRC09\_05-004-TOURNILHAC). In France, Les Laboratoires Pierre Fabre and Chugai Pharma provided additional research support for the study and Fresenius Biotech GmbH provided the ATG-Fresenius for patients who underwent allogeneic transplantation.

## Abstract

Standard first-line therapy for younger patients with peripheral T-cell lymphoma consists of six courses of CHOP or CHOEP consolidated by high-dose therapy and autologous stem cell transplantation (AutoSCT). We hypothesized that consolidative allogeneic transplantation (AlloSCT) could improve outcome.

104 patients with nodal peripheral T-cell lymphoma except ALK+ ALCL, 18 to 60 years of age, all stages and IPI scores except stage 1 and aaIPI 0, were randomized to receive 4 x CHOEP and 1 x DHAP followed by high-dose therapy and AutoSCT or myeloablative conditioning and AlloSCT. The primary endpoint was event-free survival (EFS) at three years.

After a median follow-up of 42 months, 3-year EFS of patients undergoing AlloSCT was 43% (95% confidence interval [CI]: 29%; 57%) as compared to 38% (95% CI: 25%; 52%) after AutoSCT. Overall survival at 3 years was 57% (95% CI: 43%; 71%) versus 70% (95% CI: 57%; 82%) after AlloSCT or AutoSCT, without significant differences between treatment arms. None of 21 responding patients proceeding to AlloSCT as opposed to 13 of 36 patients (36%) proceeding to AutoSCT relapsed. Eight of 26 patients (31%) and none of 41 patients died due to transplant-related toxicity after allogeneic and autologous transplantation, respectively.

In younger patients with T-cell lymphoma standard chemotherapy consolidated by autologous or allogeneic transplantation results in comparable survival. The strong graft-versus-lymphoma effect after AlloSCT was counterbalanced by transplant-related mortality. CHO(E)P followed by AutoSCT remains the preferred treatment option for transplant-eligible patients. AlloSCT is the treatment of choice for relapsing patients also after AutoSCT.

## **Introduction**

Peripheral T-cell neoplasms comprise a growing number of entities with diverse clinical, morphological, immunohistochemical, and molecular characteristics.<sup>1</sup> Except for ALK-positive anaplastic large cell lymphoma (ALCL) they mostly carry a poor prognosis.<sup>2</sup> For younger patients with T-cell lymphoma retrospective studies reported event-free survival (EFS) rates at 3 years of 48% following CHOP and 61% following CHOP plus etoposide (CHOEP)<sup>3</sup>, registry data from Sweden showed progression-free survival (PFS) and overall survival (OS) rates of 44% and 51% for transplant-eligible patients treated with CHOP and CHOEP<sup>4</sup> and the prospective cohort study COMPLETE<sup>5</sup> reported a 2-year-OS rate of 59% for patients of all ages (median 63 years) treated with doxorubicin-based, etoposide-based, or single-agent chemotherapy. Autologous or allogeneic stem cell transplantation was part of first-line therapy in 21% of these patients. All studies report significantly better survival for patients with low IPI scores (0-1) while the beneficial effect of adding etoposide to CHOP remains controversial. First-line studies combining conventional and targeted therapies either failed to show improvement<sup>6</sup> or preferentially included ALCL patients leaving unanswered the important question which patients with other T-cell lymphoma entities might benefit from this approach.<sup>7</sup> Hence, CHO(E)P consolidated with AutoSCT remains a preferred option for younger patients.<sup>8,9</sup> The largest phase 2 studies integrating AutoSCT into first-line therapy of younger T-cell lymphoma patients reported OS rates of 51% at 5 years<sup>10</sup> and 48% at 3 years<sup>11</sup>. Phase 3 studies comparing AutoSCT to alternative therapies or observation, however, have not been done and it remains unclear which patients actually benefit from this approach. Recent retrospective analyses<sup>12</sup> and data from the COMPLETE study<sup>5</sup> shed some doubts on whether AutoSCT should be offered to all patients achieving remission after induction chemotherapy. Because AlloSCT performed in patients with relapsed or refractory T-cell lymphoma gave favorable results (reviewed in<sup>13</sup>) with approximately half of patients becoming long-term survivors, we set out to compare AutoSCT with AlloSCT for consolidation of patients with T-cell lymphoma.

## **Methods**

### **Study Design and Participants**

This was a two-arm, prospective, randomized, multicenter, phase 3 trial conducted at 44 trial sites in France and Germany. It was coordinated by the French Lymphoma Study Association (LYSA) and the German Lymphoma Alliance (GLA) (former German High-grade Non-Hodgkin Lymphoma Study Group).

The study was conducted in accordance with the Helsinki declaration. The protocol and its amendment were approved by the central ethics committees in Hamburg, Germany, and by the

Agence Française de Sécurité Sanitaire des Médicaments et des Produits Biologiques (AFSSAPS ref. 2009-A00947) and Comité de Protection des Personnes, Sud-Est 6 (Ref AU 826), France, as well as local ethics committees. All patients gave written informed consent. This trial is registered with ClinicalTrials.gov, number NCT00984412.

Patients between 18 and 60 years of age with poor prognosis (stage II-IV or aaIPI >0) were eligible if they had untreated biopsy-confirmed peripheral T-cell lymphoma according to WHO classification 2008.<sup>14</sup> Local diagnoses were reviewed by expert pathologists from LYSA and GLA. Only patients with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL) anaplastic lymphoma kinase (ALK)-negative, intestinal T-/NK-cell lymphoma, hepatosplenic gamma/delta T-cell lymphoma, or subcutaneous panniculitis-like PTCL could be included. Patients with extranodal NK/ T-cell lymphoma, nasal type, were eligible before the amendment dated October 1st, 2014, and only in Germany. In France patients with extranodal NK/ T-cell lymphoma were not eligible. Other key inclusion criteria were ECOG 0-3, absence of severe cardiac dysfunction and pulmonary diffusion capacity >40% N. Key exclusion criteria were ALCL, ALK-positive, stage I disease with aaIPI 0, primary CNS involvement, ASAT, ALAT, or alkaline phosphatase > 2x N, creatinine >1.5x N, and known HIV-positivity. Full inclusion and exclusion criteria are given in supplemental table 1.

### **Randomization**

Randomization was done at a 1:1 ratio using the Pocock minimization algorithm after stratification for center, stage (I/II vs. III/IV), performance status (ECOG 0,1 vs. 2,3), serum LDH (<UNV vs. >UNV), number of extranodal sites (0,1 vs. >1) and one cycle (R)-CHO(E)P given before inclusion (no vs. yes).<sup>15</sup> Patients were registered at the trial office in Hamburg, Germany, and randomized at the data management center (Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany) by use of a computer program with an algorithm using a biased coin approach accounting for randomizations that had occurred previously. Patients were randomized up-front to receive four 14-day cycles of CHOEP, one course of DHAP and AutoSCT or AlloSCT. Patients with CR, CRu, PR, or stable disease (SD) at the time of re-staging continued on study and were to receive either BEAM (BCNU, etoposide, cytosine-arabioside, melphalan) high-dose chemotherapy followed by transplantation of autologous hematopoietic stem cells (AutoSCT) or myeloablative conditioning with fludarabine, busulfan, and cyclophosphamide (FBC) followed by transplantation of allogeneic hematopoietic stem cells (AlloSCT).<sup>16</sup>

### **Procedures**

Patients had baseline assessment including history, clinical characteristics, laboratory tests, MRI or CT scans of neck, thorax, abdomen, and a bone marrow biopsy. PET scans were not mandatory. Figure 1 shows the trial profile. CHOEP comprised cyclophosphamide ( $750 \text{ mg/m}^2$ ), doxorubicin ( $50 \text{ mg/m}^2$ ), and vincristine (2 mg), administered intravenously (IV) on day 1, etoposide ( $100 \text{ mg/m}^2$ , IV, on days 1-3) and oral prednisone (100 mg) administered on days 1 to 5.

All patients were to receive four courses of CHOEP at 2-week-intervals with G-CSF support from day 4 -13. Two weeks after cycle 4 of CHOEP a formal restaging including physical examination, blood counts and chemistry, electrocardiogram, and CT scans of neck, thorax, and abdomen was performed. Response was evaluated according the 1999 consensus criteria.<sup>17</sup> Patients with CR, CRu, PR, or SD, no active infection or severe organ toxicity proceeded to one course of DHAP as soon as leukocytes ( $>2500/\text{mm}^3$ ) and platelets ( $>80.000/\text{mm}^3$ ) had recovered. DHAP consisted of dexamethasone (3 x 8 mg orally or IV on days 1-4), cytosine-arabioside ( $2000 \text{ mg/m}^2$ , twice daily IV on day 2), and cis-platinum ( $100 \text{ mg/m}^2$ ) or carboplatinum (AUC 5), both IV on day 1). For patients randomized to AutoSCT or AlloSCT but not finding a suitable donor prior to the planned transplant date, collection of autologous peripheral blood stem cells was started two weeks after DHAP. A minimum of  $4 \times 10^6$  CD 34-positive cells per kg body weight was required to continue study treatment. For patients randomized to AlloSCT search for an HLA-identical matched sibling or unrelated donor started immediately after randomization. In France, only fully matched (10/ 10 HLA loci) family or unrelated donors were accepted while in Germany donors compatible at 9 of 10 loci were accepted. Collection of allogeneic stem cells followed local protocols.

High-dose chemotherapy prior to AutoSCT consisted of BCNU ( $300 \text{ mg/m}^2$ ) on day -7, cytosine-arabioside ( $200 \text{ mg/m}^2$ , twice daily) on days -6 to -3, etoposide ( $200 \text{ mg/m}^2$ ) on days -6 to -3, and melphalan ( $140 \text{ mg m}^2$ ) on day -2. Patients randomized to AlloSCT finding an HLA-compatible donor were conditioned with fludarabine ( $25 \text{ mg/m}^2$  IV) on days -8 to -4, busulfan ( $4 \times 1 \text{ mg/kg}$  body weight orally or  $4 \times 0.8 \text{ mg/kg}$  body weight IV) on days -6 to -4, and cyclophosphamide IV ( $60 \text{ mg/kg}$  body weight) on days -3 and -2. Autologous or allogeneic blood stem cells were transplanted on day 0. Prophylaxis of graft-versus-host disease (GvHD) consisted of anti-thymocyte globulin (ATG-Fresenius), ( $10 \text{ mg/kg}$  body weight IV) on days -4 to -2, mycophenolate mofetil ( $1000 \text{ mg}$  orally or IV, twice daily) days +1 to +28, and cyclosporine A starting on day -1 until day +100. Tapering of GvHD prophylaxis depended on the presence and severity of acute GvHD. ECOG performance status and all adverse events were retrieved in predefined categories from case report forms using National Cancer Institute Common Toxicity Criteria (version 3.0).<sup>18</sup>

## Statistical Analysis



The trial was planned to detect an improvement of event-free survival (EFS) at three years from 35% achieved with AutoSCT to 60% by AlloSCT in the intent-to-treat population (full analysis set). Using the nQuery Advisor, version 2.0, the planned sample size for the primary endpoint EFS at three years was 140 patients (including a 10% loss of patients) in order to detect this difference at a power of 80% and an  $\alpha$ -error of 5%, two sided (hazard ratio HR = 0.487).

Secondary endpoints included complete remission rate, rate of primary progression, relapse rate, rate of patients proceeding to transplantation, incidence of acute and chronic GvHD after AlloSCT, rate of treatment related deaths, overall survival (OS), progression-free survival (PFS), as well as safety and tolerability. EFS was calculated as time from randomization to disease progression, start of salvage treatment, start of any additional, unplanned treatment, response categorized as stable disease or unknown, relapse, or death from any cause. Progression-free survival (PFS) was defined as time from randomization to progression, relapse, or death from any cause. Overall survival (OS) was defined as time from randomization to death from any cause. Patients with no event reported at the time of analysis were censored at the most recent assessment date. Kaplan-Meier curves were drawn and log-rank tests were calculated.<sup>19, 20</sup> Three-year-rates of EFS, PFS, and OS with 95% confidence intervals (CI) were determined. A Cox multivariate regression model was used to test whether therapeutic effects emerging from univariate analyses remained stable after adjustment for main strata. Estimates are given as hazard ratios with 95% CI and corresponding p values. Differences between groups were classified as significant for p values less than or equal to 0.050. Patient characteristics were analyzed by use of  $\chi^2$  test and, if necessary, by Fisher's exact test. Statistical analyses were done with IBM SPSS 25 and 26 software. Cumulative incidence curves for time to relapse and time to non-relapse mortality are presented using R (version 3.1.0, package 'cuminc').<sup>21</sup>

The primary endpoint and major secondary endpoints were calculated for all patients randomized (intent-to-treat). Because we expected that 30-35% of patients would not reach transplantation or find a compatible donor additional explorative analyses were planned. First, we analyzed all transplanted patients as treated; second, we analyzed all transplanted patients as randomized.

## **Results**

### **Patients**

From March 2011 to July 2014, 104 patients were included in the trial at 17 German and 27 French centers. The data safety and monitoring board (DSMB) in agreement with the study steering committee stopped randomization and recruitment in August 2014 because a planned interim analysis had shown that it was highly unlikely to meet the primary endpoint. The transplant-related mortality observed contributed to this decision.

One patient did not receive any study treatment leaving 103 patients for the intention-to-treat analysis. Fifty-four patients were assigned to AutoSCT and 49 patients to AlloSCT (Figure 1). Baseline patient characteristics were well balanced without significant differences between treatment arms. According to primary pathology 41 patients (40 %) had PTCL-NOS, 35 patients (34 %) had AITL, and 15 patients (15 %) had ALCL, ALK-negative. Ten patients (10%) suffered from other T-cell lymphoma subtypes and two patients had T-cell lymphoma without further specification.

Reference pathology review was performed in 97% of patients (Table 1).

### **Treatment**

Thirty-four of 54 patients (63%) randomized to AutoSCT actually received it; 20 patients could not proceed to transplantation because of early progression (15 patients), change of diagnosis (non-PTCL) (3 patients), toxicity, or patient's decision (one patient each). Twenty-six of 49 randomized patients (53%) underwent AlloSCT while 15 patients did not complete all chemotherapy because of early progression (14 patients), or change of diagnosis (one patient). Eight patients randomized to AlloSCT were rescheduled to receive AutoSCT, one by DSMB decision and seven because no compatible donor had been found. The diagnoses of patients without a donor were PTCL-NOS (3 patients), AITL (2 patients) and ALCL, ALK negative (2 patients). One patient with AITL could not receive AutoSCT because of mobilization failure.

Finally, 41 patients were autografted and 26 patients had an allograft. The median duration of all chemotherapy from day 1 of the first course of CHOEP until the day of transplantation was 107 days in the AutoSCT arm, and 119 days in the AlloSCT arm of the study. This difference was significant ( $p=0.011$ ). The median time interval between the last course of CHOEP and transplantation was 64 days in the AutoSCT and 70 days in the AlloSCT arm of the study. Patients receiving an autologous transplant had a median of  $5.0 \times 10^6$  CD34+ cells /kg body weight (range: 2.3-25.8) infused and recovered leukocytes to  $>1 \times 10^9$ /L on day +10 (quartiles: day 9; day 12). Platelet recovery  $> 20 \times 10^6$ /L was observed on day 11 (7; 13). Twenty-six patients receiving AlloSCT had  $6.6 \times 10^6$  CD34+ cells/ kg

body weight (2.0-13.6) infused. They recovered leukocytes at day +13 (12; 16) and platelets at day +12 (9; 14) (Supplemental Table 2).

### **Efficacy**

By intent-to-treat analysis, twenty-five of 49 patients (51%) in the AlloSCT arm and 21 of 54 patients (39%) in the AutoSCT arm achieved a CR/CRu after end of all therapy. A partial remission (PR) was achieved by four patients (8%) in the AlloSCT arm and nine (17%) in the AutoSCT arm. Stable disease was diagnosed in two patients after AutoSCT; it was not reported after AlloSCT. After CR, CRu, or PR had been achieved, relapse was recorded in nine patients in the AutoSCT arm and four patients in the AlloSCT arm. One patient in the AutoSCT arm and 8 patients in the AlloSCT arm died after CR, CRu and untreated PR (Table 2).

Overall, eighteen of all patients (33%) randomized to AutoSCT and 21 of all patients (43%) randomized to AlloSCT have died. Causes of death were progression or relapse of lymphoma in 13 patients (72%) of the AutoSCT arm versus eleven patients (52%) of the AlloSCT arm. Salvage treatment-related death was recorded in four patients of the AutoSCT arm and in two patients of the AlloSCT arm. No patient died due to AutoSCT. Eight patients (38%) died study-treatment-related in the AlloSCT arm. No other causes of death except for one patient dying of secondary neoplasia in the AutoSCT arm were reported. For a complete list of causes of death in the intent-to-treat population and patients who actually received a transplant see Supplemental Table 3.

With a median follow-up of 42 months (range: 0.2 – 74 months) EFS, PFS, and OS showed no significant differences between treatment arms. The 3-year EFS was 43% (95% CI: 29%; 57%) for patients randomized to AlloSCT and 38% (95%CI: 25%; 52%) for patients randomized to AutoSCT (Figure 2A). The 3-year PFS was 43% (95% CI: 29%; 57%) in the AlloSCT arm versus 39% (95%CI: 26%; 52%) in the AutoSCT arm (Figure 2B). The 3-year OS was 57% (95% CI: 43%; 71%) in the AlloSCT versus 70% (95% CI: 57%; 82%) in the AutoSCT arm (Figure 2C).

Multivariate analyses (AlloSCT vs. AutoSCT), adjusted for main strata, confirmed these results (hazard ratio  $HR_{EFS}$ : 0.9 ([95% CI: 0.6 – 1.5];  $p=0.721$ ),  $HR_{PFS}$ : 0.9 ([95% CI: 0.5 – 1.5];  $p=0.702$ ),  $HR_{OS}$ : 1.3 ([95% CI: 0.7 – 2.4];  $p=0.421$ ). LDH > normal was found as significant risk factor for EFS ( $HR_{EFS}$ : 2.3;  $p=0.004$ ), and PFS ( $HR_{PFS}$ : 2.4;  $p=0.003$ ) (Table 3).

As only 67 patients (65%) could receive therapy as per protocol we did pre-planned subgroup analyses restricted to patients actually receiving autologous or allogeneic transplantation. Forty of 41 patients proceeding to AutoSCT and 23 of 26 patients given AlloSCT had achieved CR, CRu, or PR after four courses of CHOEP. Sixteen patients of both treatment arms had reached CR or CRu. Three patients who reported SD after 4 courses of CHOEP achieved CRu, PR, and PR after AlloSCT while the

only patient with SD after CHOEP undergoing AutoSCT showed CR after transplantation. The remission status of transplanted patients immediately prior to transplantation is unknown because the study protocol did not stipulate for another re-staging after CHOEP and DHAP chemotherapy. The 3-year EFS for the 26 patients who actually received AlloSCT was 65% (95% CI: 47%; 84%) as compared to 57% (95% CI: 42%; 73%) for the 41 patients receiving AutoSCT. PFS and OS for allografted patients was identical at 65% (95% CI: 47%; 84%); PFS and OS for autografted patients was 57% (95% CI: 42%; 73%) and 81% (95% CI: 68%; 93%). None of these differences were significant (Figure 2 D-F). With a median observation time of 42 months, none of 21 patients who had achieved CR, CRu, or PR relapsed after AlloSCT in contrast to 13 of 36 (36%) patients who relapsed after AutoSCT (Table 2). One patient died from a secondary neoplasia after AutoSCT while eight patients (31%) died transplant-related after AlloSCT (Supplemental Table 3). Cumulative incidence of relapse for patients who had achieved CR, CRu, or PR at final restaging was 17% (95% CI: 4%; 29%) after AutoSCT vs. 0% after AlloSCT at 1 year and 40% (95% CI: 22%; 58%) vs. 0% at 3 years after transplantation. Cumulative incidence of non-relapse mortality was 0% in auto-grafted vs. 23% (95% CI: 6%; 40%) in allografted patients at 1 year. (Figure 3). TRM after AlloSCT was mostly associated with acute or chronic GvHD (Supplemental Table 4). The incidence and severity of acute and chronic GvHD is shown in Supplemental Table 5.

### **Safety**

103 patients started study treatment with CHOEP chemotherapy. Incidence and severity of adverse events occurring with CHOEP and DHAP did not differ by treatment arm. (Supplemental Table 6 and 7). Adverse events CTC grades 3 – 5 occurring after BEAM high-dose therapy and AutoSCT or FBC conditioning and allogeneic transplantation are summarized in Table 4. The infections after CHOEP as well as after AutoSCT and AlloSCT are detailed in Supplemental Table 8 and 9.

Nineteen of 26 patients (73%) submitted to AlloSCT suffered GvHD.<sup>17</sup> The maximum grade of acute GvHD was > 2 in 7 patients; two of these patients died. Chronic GvHD occurred in 8 patients, it was described as limited disease in 7 patients.<sup>18</sup> One patient died of chronic GvHD and complications.

Three secondary neoplasms (3%) were observed: one aggressive B-cell lymphoma after AlloSCT and two solid tumors after AutoSCT.

## **Discussion**

We report that consolidation with high-dose therapy and AutoSCT or myeloablative conditioning and AlloSCT in younger patients with poor-risk T-cell lymphomas showed no significant differences in EFS, PFS, and OS.

For the 54 patients randomized to AutoSCT the 3-year PFS of 39% is between the 36% reported by a German consortium and the 48% reported by the Nordic Lymphoma Group<sup>10,11</sup>. The reason for the excellent OS (70%), especially for patients in the AutoSCT arm may be partly explained by differences in the percentages of T-cell lymphoma entities treated or in the individual patient characteristics between studies. New drugs inducing further remissions resulting in a tentatively higher percentage of patients able to proceed to AlloSCT after failure of AutoSCT may also have their roles. Actually, fourteen of 33 patients (42%) randomized to AutoSCT but refractory to chemotherapy or relapsing after AutoSCT were finally allografted. Long-term follow up of study patients is planned and will shed further light on the important question which role AlloSCT has to play in primary refractory patients and patients relapsing after AutoSCT.

There is only one other study reporting on allogeneic transplantation as part of first-line therapy of T-cell lymphoma.<sup>24</sup> Corradini et al. treated 61 younger patients with inclusion criteria similar to our study. Twenty-three patients achieving CR or PR after chemotherapy underwent AlloSCT after reduced intensity conditioning with thiotepa, fludarabine, and cyclophosphamide. Fourteen patients lacking a suitable donor received AutoSCT, all other patients (38%) went off study before transplantation. In this study, three of 23 patients (13%) experienced non-relapse mortality, 4 patients relapsed (17%) after AlloSCT. Lower non-relapse mortality has repeatedly been reported after reduced-intensity conditioning, in many instances counterbalanced by a higher relapse rate. A retrospective registry study suggested similar outcomes for patients allografted after myeloablative or reduced-intensity conditioning.<sup>25</sup> In our study, the 26 patients who underwent myeloablative conditioning followed by AlloSCT did not experience any relapse; however, NRM was higher than reported by Corradini et al.

This phase 3 study and the phase 2 studies on autologous or allogeneic transplantation cited above gave comparable OS- and PFS-rates. Although survival of our patients did not significantly differ when only patients actually receiving AutoSCT or AlloSCT were compared, it is interesting to note that EFS and PFS curves for patients after AlloSCT reach a plateau about two years after transplantation while relapses continue to occur in autografted patients. Similar observations have been made in the Nordic trial reporting relapses later than two years post AutoSCT in 7% of the intent-to-treat population.<sup>10</sup>

Although the primary endpoint was not met our study has major implications for clinical practice and future studies. First of all, more than one third of patients were unable to proceed to transplantation mostly because of early progression or relapse. Similar observations have been made in all T-cell lymphoma studies investigating first-line chemotherapy.<sup>10, 11, 24</sup> In future trials patients with up-front chemo-refractory disease should be spared toxic but ineffective chemotherapy. Studies identifying chemorefractory patients by innovative molecular approaches will not only contribute to a better understanding of T-cell lymphoma pathophysiology but help in designing new trials involving targeted therapies.

It is important to note that our study did not ask for regular PET scans. Nowadays, PET / CT is routinely used in patients with T-cell lymphoma and interim PET plays an important role to identify refractory patients and change treatment as early as possible.<sup>26</sup>

In our study many patients progressed towards the end of chemotherapy right before transplantation. Changing chemotherapy from CHOEP to DHAP did not alleviate but may have aggravated the problem. The ECHELON-2 study reported promising results with CHP + brentuximab vedotin (BV) as compared to CHOP for first-line therapy of patients with CD30-positive ALCL and other T-cell lymphomas.<sup>7</sup> To what extent the inclusion of BV into first-line therapy may help to bring more patients to AutoSCT is not yet clear because AutoSCT was not part of the study protocol and few patients only received a transplant. In our study, the median time interval between the last course of CHOEP and transplantation was 64 days in the AutoSCT and 70 days in the AlloSCT arm and thus substantially longer than planned. Such delays seem to be detrimental to patients with T-cell lymphomas and could be reduced by using haplo-identical donors for AlloSCT. Early results of haplo-identical transplantation in (T-cell) lymphoma seem promising.<sup>27, 28</sup> Restricting chemotherapy to 2-3 cycles followed by immediate AlloSCT could be another option to reduce the number of early treatment failures.

Except for two cases of secondary tumors relapse remains the major problem after AutoSCT. At least for patients with ALCL this problem may be addressed by the administration of BV post AutoSCT. In patients with Hodgkin lymphoma this strategy helped to significantly reduce posttransplant relapses.<sup>29</sup> Patients after AlloSCT showed a completely different pattern of failure: typical complications of allogeneic transplantation, mostly associated with acute or chronic GvHD, resulted in significant transplant-related morbidity and mortality. Among others, the myeloablative conditioning used in this study may have contributed to the relatively high TRM observed. . Although this study demonstrates a remarkably strong graft vs. lymphoma effect in patients with T-cell lymphoma allografted in first remission we believe that a TRM of 31% is not acceptable in 2020 because new drugs may induce further albeit short-lived remission(s) in patients failing AutoSCT

thereby increasing their chance to proceed to AlloSCT at later stages. Thus, although further refinement in donor selection, conditioning, GvHD prophylaxis and treatment, or routine use of haplo-identical transplantation, may improve results, we for the time being recommend to reserve AlloSCT for patients failing AutoSCT and patients with the earliest signs of progression or relapse. Economic considerations may also support this notion.

Meanwhile, further search for more effective drugs and cellular therapies in T-cell lymphoma is highly warranted.<sup>30</sup>

In conclusion, standard chemotherapy followed by high-dose therapy and autologous transplantation remains a preferred option for younger patients with peripheral T-cell lymphoma.

Allogeneic transplantation can achieve long-term survival also after failure of autologous transplantation and, therefore, is considered the treatment of choice for patients with relapsed or refractory disease.

## **Acknowledgements**

We thank the patients, families, caregivers and all investigators from France and Germany who participated in this clinical trial, the French Lymphoma Study Association (LYSA) and the German Lymphoma Alliance (GLA),

the expert pathologists who provided histopathological review: Andreas Rosenwald, M.D., (chairman), Wuerzburg; Alfred C. Feller, M.D., Luebeck; Martin-Leo Hansmann, M.D., Frankfurt; Wolfram Klapper, M.D., Kiel; Peter Moeller, M.D., Ulm; Hans Konrad Mueller-Hermelink, M.D., Wuerzburg; Harald Stein, M.D., Berlin, all in Germany; Laurence de Leval, M.D., Lausanne, Switzerland, Philippe Gaulard M.D., Paris, Marie Parrens M.D., Bordeaux, Albane Ledoux-Pilon M.D., Clermont-Ferrand, Céline Bossard M.D., Nantes, Nadine Vailhen, Creteil and the LYSAP platform, all in France,

the data and safety monitoring committee that served as an independent expert advisory group to evaluate safety and efficacy data during the trial, including Hildegard Greinix, M.D., Graz, Austria; Anthony H. Goldstone, M.D., London, United Kingdom; Vincent Levy, M.D., Bobigny, France and Ephraïm P. Hochberg M.D., Boston, United States of America,

all members of the study trial offices in Hamburg, Germany, including K. Kocksch, and B. Freymark, in Göttingen, Germany, including K. Menck, PhD, and E. Stitz, in Clermont-Ferrand, France, including Christelle Latière, Aurélie Cabrespine, Gérald Gouby, Lise Laclautre Pharm. D., Richard Lemal M.D. and Sébastien Bailly M.D. as well as the members of Clinical Research Organisation of the FILO group including Roselyne Delepine, Alexandra Fayault and Valérie Rolland for their support,

the data centre Leipzig, Germany, (chair: Markus Loeffler MD, PhD) including: Sigrid Haupt, Jürgen Hentschel, Martina Kunert, Beate Mann, Katja Rillich PhD, Ulrike Schoenwiese, Barbara Wicklein.

We thank the principal investigators in France and Germany: Angers: Marie Pierre Moles, Avignon: Borhane Slama, Besançon: Adrien Chauchet, Béziers: Alain Saad, Bordeaux (Polyclinique Bordeaux Nord Aquitaine): Olivier Fitoussi, Corbeil: Alain Devidas, La Roche Sur Yon: Mourad Tiab, Mulhouse: Bernard Drenou, Nantes: Jean Luc Harousseau, Nimes: Eric Jourdan, Saint Louis: Pauline Brice, Saint Cloud-Institut Curie: Sylvie Glaisner, Saint Etienne: Jérôme Cornillon  
Mannheim: Stefan Klein, Marburg: Andreas Neubauer, Moenchengladbach: Ullrich Graeven.

## **Author contributions**

Study conception and design: NS, OT, LT, MZ, BG, MN, CG

Collection and assembly of data: All authors

Data analysis and interpretation: BA, MZ, NS, OT



Provision of study materials or patients: All authors

Drafting or revising the manuscript: NS, BA, MZ, MN, OT, BF

Review and approval of the final version of the manuscript: All authors

### **Declaration of interest**

Grants: Norbert Schmitz and Lorenz Truemper: Bundesministerium für Bildung und Forschung (BMBF, FKZ 01KG0705),

Olivier Tournilhac: Ministère de la Santé et des Solidarités (PHRC09\_05-004-TOURNILHAC). In France, Les Laboratoires Pierre Fabre and Chugai Pharma provided additional research support for the study and Fresenius Biotech GmbH provided the ATG-Fresenius for patients who underwent allogeneic transplantation.

Relevant financial activities outside the submitted work:

Personal Fees: N. Schmitz: Riemsler, Janssen, Kite/ Gilead, Novartis, Takeda; L. Truemper: Takeda; Janssen Cilag, BMS, Gilead, Takeda, Amgen, Hexal, Celgene, Astra Zeneca; P. Reimer: Takeda, Novartis, Sanofi-Aventis, BMS; A. Viardot: Roche, Kite/Gilead, Pfizer, BMS, Amgen; V. Poeschel: Abbvie, Amgen, Roche; M.Haenel: Amgen, Roche, Takeda, Novartis.

Non-financial support:

All other authors declared no conflicts of interest.

Data sharing

For original data and protocol, please email the corresponding author.

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## Tables

**Table 1. Demographics and disease characteristics for randomized patients and for transplanted patients only.**

**Table 2. Treatment response for randomized patients and for transplanted patients only.**

**Table 3. Multivariate analysis of event-free, progression-free, and overall survival adjusted for strata.**

**Table 4. Non-hematological adverse events grade 3-5 following BEAM/ AutoSCT and FBC/ AlloSCT.**

**Table 1:** Demographics and disease characteristics for randomized patients and for transplanted patients only.

	Randomized patients		Transplanted patients	
	AutoSCT n=54	AlloSCT n=49	AutoSCT <sup>#</sup> n=41	AlloSCT n=26
Male	31 (57%)	34 (69%)	28 (68%)	17 (65%)
Female	23 (43%)	14 (31%)	13 (32%)	9 (35%)
Age, median (range)	50 (28, 60)	50 (24, 60)	51 (24, 60)	50 (35, 60)
LDH > N	33 (61%)	30 (61%)	22 (54%)	11 (42%)
ECOG > 1	11 (20%)	10 (20%)	8 (20%)	5 (19%)
Stage III / IV	47 (87%)	44 (90%)	36 (88%)	23 (88%)
aalPI 0	2 (4%)	3 (6%)	1 (2%)	3 (12%)
aalPI 1	22 (41%)	16 (33%)	20 (49%)	10 (38%)
aalPI 2	21 (39%)	22 (45%)	14 (34%)	10 (38%)
aalPI 3	9 (17%)	8 (16%)	6 (15%)	3 (12%)
E-involvement	32 (59%)	31 (63%)	24 (59%)	15 (58%)
E > 1	16 (30%)	17 (35%)	11 (27%)	6 (23%)
IPI 0	2 (4%)	3 (6%)	1 (2%)	3 (12%)
IPI 1	16 (30%)	10 (20%)	14 (34%)	7 (27%)
IPI 2	22 (41%)	21 (43%)	16 (39%)	11 (42%)
IPI 3	9 (17%)	11 (22%)	9 (22%)	4 (15%)
IPI 4	5 (9%)	4 (8%)	1 (2%)	1 (4%)
Bulky disease	10 (19%)	7 (14%)	8 (20%)	3 (12%)
B-symptoms	32 (59%)	29 (59%)	23 (56%)	16 (62%)
Bone marrow involved	17 (31%)	15 (31%)	7 (17%)	9 (35%)
<b>Histology</b>				

Reviewed	54* (100%)	46 (94%)	41** (100%)	25 (96%)
Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)	16 (30%)	15 (33%)	11 (27%)	8 (32%)
Angioimmunoblastic T-cell lymphoma	17 (33%)	20 (43%)	16 (40%)	12 (48%)
Anaplastic large cell lymphoma ALK-negative	9 (17%)	5 (11%)	8 (20%)	3 (12%)
Extranodal NK/T-cell lymphoma, nasal type	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Enteropathy-associated T-cell lymphoma (EATL) types I and II	3 (6%)	0 (0%)	3 (8%)	0 (0%)
Hepatosplenic T-cell lymphoma	2 (4%)	1 (2%)	1 (2%)	1 (4%)
Subcutaneous panniculitis-like PTCL	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Primary cutaneous gamma/delta T-cell lymphoma	0 (0%)	1 (2%)	0 (0%)	0 (0%)
T-cell lymphoma, further specification not possible	1 (2%)	1 (2%)	1 (2%)	1 (4%)
Other entities	3*** (6%)	2**** (4%)	0 (0%)	0 (0%)

# seven patients randomized to AlloSCT are included

\* two patients and \*\* one patient without definitive diagnosis (suspicious of PTCL, no definite diagnosis possible)

\*\*\* T-cell histocyte-rich large B-cell lymphoma; histiocytic sarcoma; classical Hodgkin lymphoma

\*\*\*\* lymph node infiltration by primary cutaneous T-cell lymphoma (e.g. Mycosis fungoides); EBV-positive, CD30-positive lymphoproliferation

**Table 2:** Treatment response according to treatment arms for randomized patients and transplanted patients only.

	Randomized patients		Transplanted patients	
	AutoSCT n=54	AlloSCT n=49	AutoSCT <sup>#</sup> n=41	AlloSCT n=26
<b>Treatment Response Rates with [95% CI]</b>				
CR/CRu	21/54 (39%) [26%; 53%]	25/49 (51%) [36%; 66%]	26/41 (63%) [47%; 78%]	19/26 (73%) [52%; 88%]
CR/CRu/untreated PR	30/54 (56%) [41%; 69%]	28/49 (57%) [42%; 71%]	36/41 (88%) [74%; 96%]	21/26 (81%) [61%; 93%]
Relapse after CR/CRu	7/21 (33%) [15%; 57%]	3/25 (12%) [ 3%; 31%]	10/26 (38%) [20%; 59%]	0/19 (0%) [ 0%; 18%]
Relapse after CR/CRu/untreated PR	9/30 (30%) [15%; 49%]	4/28 (14%) [ 4%; 33%]	13/36 (36%) [21%; 54%]	0/21 (0%) [ 0%; 16%]
<b>EFS events:</b>				
PD at the end of therapy	19 (35%)	16 (33%)	5 (12%)	1 (4%)
Relapse after CR, CRu	7 (13%)	3 (6%)	10 (24%)	0 (0%)
Relapse after untreated PR	2 (4%)	1 (2%)	3 (7%)	0 (0%)
Treated PR	0 (0%)	1* (2%)	0 (0%)	0 (0%)
SD	2** (4%)	0 (0%)	0 (0%)	0 (0%)
Unknown	3* (6%)	0 (0%)	0 (0%)	0 (0%)
Death after CR, CRu, untreated PR	1 (2%)	8 (16%)	1 (2%)	8 (31%)
<b>EFS, PFS, OS rates with [95% CI]</b>				
3-year EFS	38% [25%; 52%]	43% [29%; 57%]	57% [42%; 73%]	65% [47%; 84%]
3-year PFS	39% [26%; 52%]	43% [29%; 57%]	57% [42%; 73%]	65% [47%; 84%]
3-year OS	70% [57%; 82%]	57% [43%; 71%]	81% [68%; 93%]	65% [47%; 84%]

<sup>#</sup> seven patients randomized to AlloSCT are included

\* patients non PTCL

\*\* death after salvage treatment

CI=confidence interval. CR=complete response. CRu=unconfirmed complete remission. PR=partial response. PD=progressive disease. SD= stable disease. EFS=event-free survival. PFS=progression-free survival. OS=overall survival.

**Table 3:** Multivariate analysis of event-free, progression-free, and overall survival adjusted for strata.

	<b>EFS</b> <b>HR (95% CI)</b>	<b>p</b>	<b>PFS</b> <b>HR (95% CI)</b>	<b>p</b>	<b>OS</b> <b>HR (95% CI)</b>	<b>p</b>
<b>Randomized patients</b>						
AlloSCT vs. AutoSCT	0.9 (0.6-1.5)	0.721	0.9 (0.5-1.5)	0.702	1.3 (0.7-2.4)	0.421
LDH > N	2.3 (1.3-4.1)	0.004	2.4 (1.4-4.4)	0.003	2.0 (1.0-4.3)	0.064
ECOG > 1	1.0 (0.5-1.8)	0.901	1.0 (0.5-1.8)	0.977	1.2 (0.6-2.5)	0.648
Stage III/IV	1.0 (0.4-2.2)	0.918	1.1 (0.5-2.6)	0.844	1.4 (0.4-4.8)	0.546
E > 1	1.2 (0.7-2.1)	0.492	1.2 (0.7-2.2)	0.429	1.0 (0.5-1.9)	0.896
<b>Transplanted patients</b>						
AlloSCT vs. AutoSCT <sup>#</sup>	0.8 (0.3-1.7)	0.513	0.8 (0.3-1.7)	0.513	1.8 (0.7-4.6)	0.218
LDH > N	1.4 (0.6-3.1)	0.455	1.4 (0.6-3.1)	0.455	1.0 (0.3-3.0)	0.977
ECOG > 1	1.1 (0.4-2.8)	0.886	1.1 (0.4-2.8)	0.886	2.3 (0.8-7.0)	0.140
Stage III/IV	1.3 (0.4-4.5)	0.645	1.3 (0.4-4.5)	0.645	1.2 (0.3-5.4)	0.807
E > 1	0.6 (0.2-1.7)	0.341	0.6 (0.2-1.7)	0.341	0.5 (0.1-1.8)	0.273

<sup>#</sup> seven patients randomized to AlloSCT are included



**Table 4:** Non-hematological adverse events grade 3-5 following BEAM/ AutoSCT and FBC/ AlloSCT. For details on infections see supplemental table 9.

	Transplanted patients	
	BEAM/ AutoSCT <sup>#</sup> n=41	FBC/ AlloSCT n=26
Nausea	2/40 (5%)	2/26 (8%)
Vomiting	1/40 (2%)	1/26 (4%)
Diarrhea	4/40 (10%)	3/26 (12%)
Constipation	0/41 (0%)	0/26 (0%)
Mucositis/ stomatitis	13/41 (32%)	6/26 (23%)
Cardiac arrhythmia	1/40 (2%)	1/25 (4%)
Cardiac general	1/41 (2%)	0/26 (0%)
Hemorrhage/ bleeding	2/41 (5%)	1/26 (4%)
Renal/ genitourinary	0/41 (0%)	4/26 (15%)
Neuropathy sensory	0/41 (0%)	0/26 (0%)
Mood alteration	0/41 (0%)	1/26 (4%)
Allergic reaction/ hypersensitivity	0/40 (0%)	0/26 (0%)
Infections	13/41 (32%)	10/26 (38%)
Hepatotoxicity (other than VOD)	-	1/26 (4%)
VOD (venous occlusive disease)	-	0/26 (0%)

<sup>#</sup> seven patients randomized to AlloSCT are included

## Figure legends

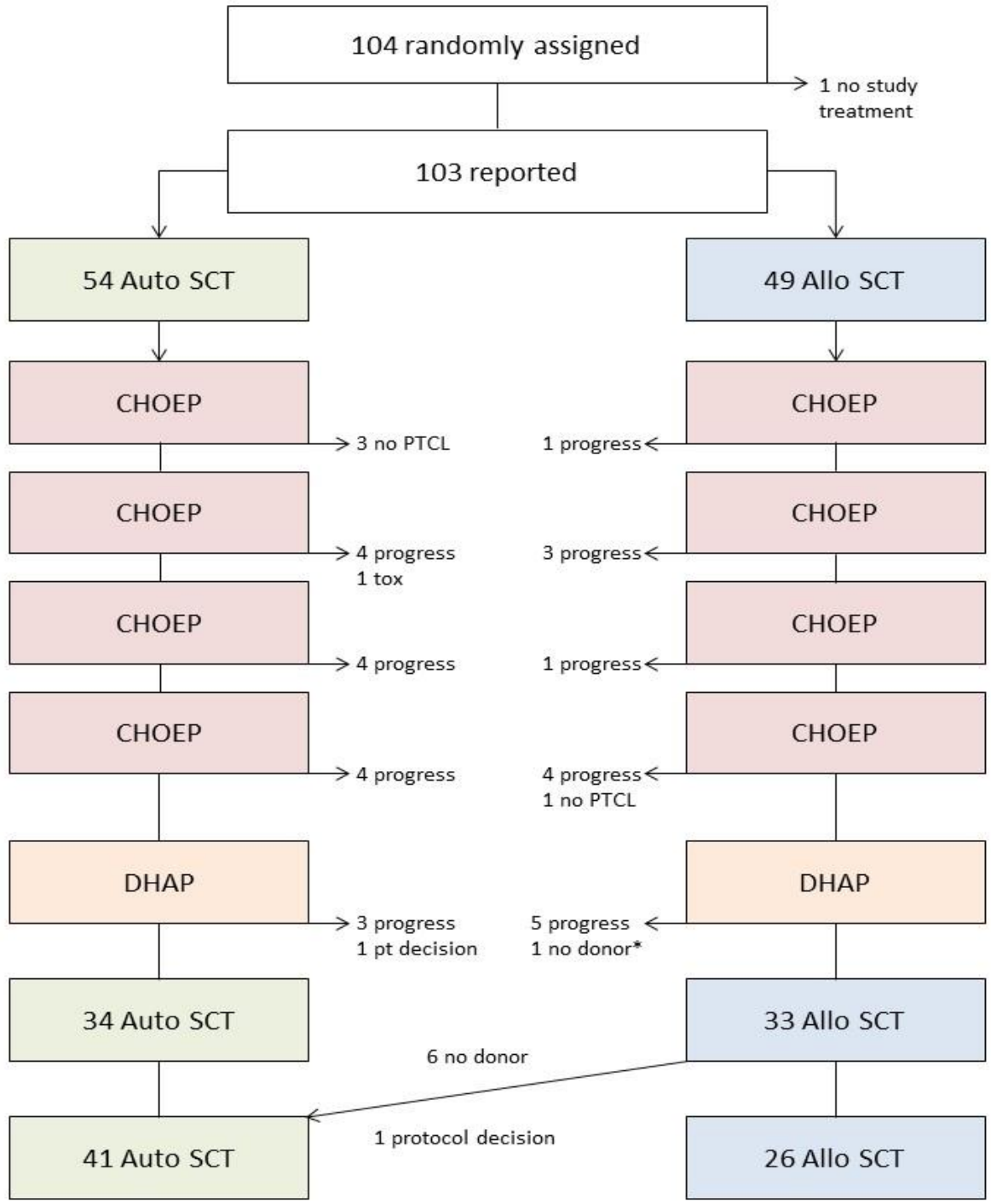
### Figure 1. CONSORT diagram.

Auto SCT = autologous transplantation. Allo SCT = allogeneic transplantation. CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone. DHAP = dexamethasone, cytosine-arabioside, cis-platinum or carboplatinum. mob. fail. = mobilization failure. no PTCL = no PTCL according reference pathology.

Figure 2. Event- free (A, D), progression-free (B, E), and overall survival (C, F) according to treatment arms for all randomized patients (intent-to-treat population) (A, B, C) and for transplanted patients only (D, E, F).

Figure 3. Cumulative incidence for relapse (A) and non-relapse mortality (B).

Figure 1



\* no auto SCT due to mobilization failure

Figure 2

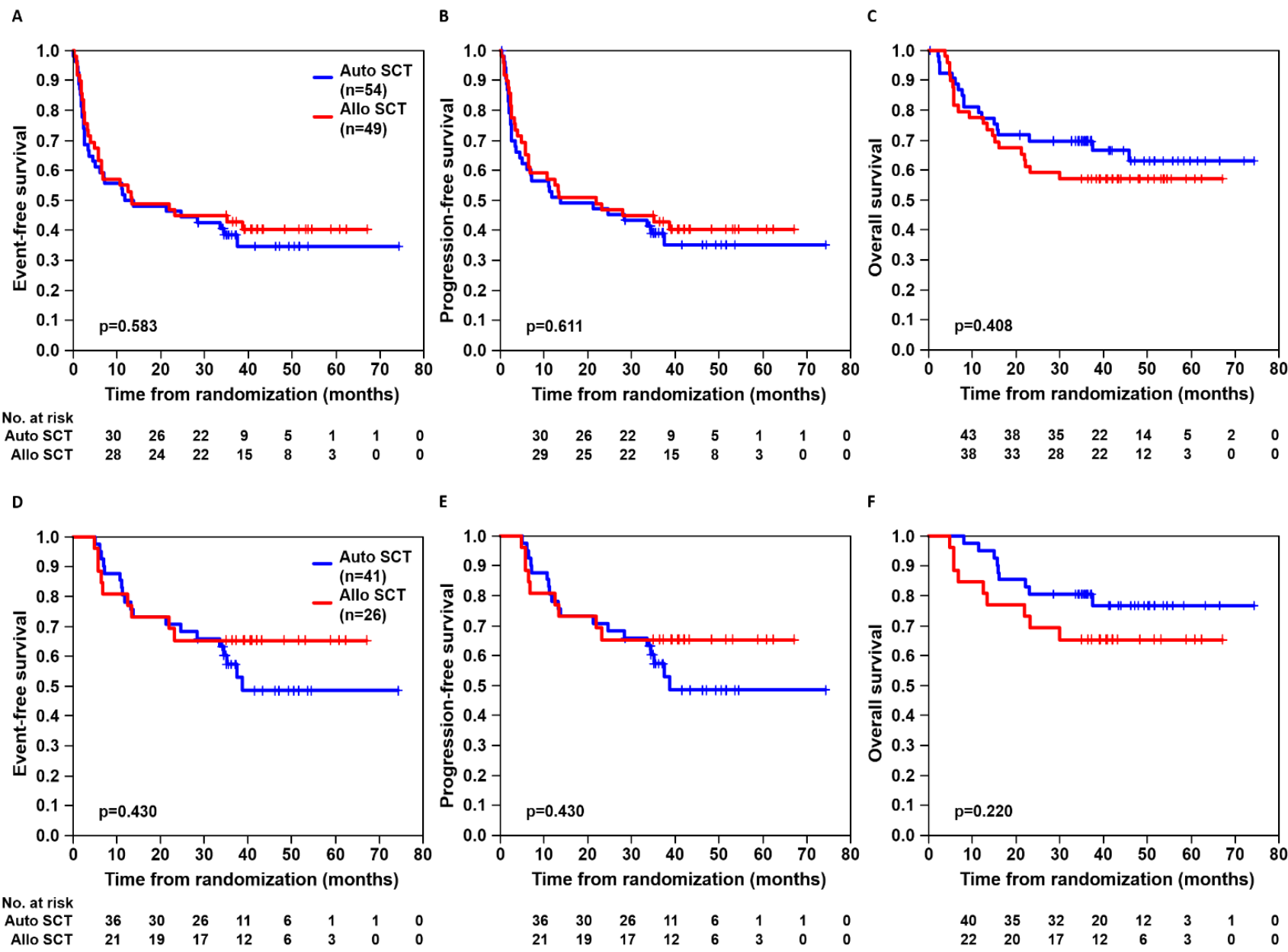


Figure 3

