Short title: DSHNHL 2006-1A (AATT)

Study medication: none

Eudra-CT Number: 2007-001052-39

Register-Number: 00270

Clinical study report (gemäß ICH E3 – *ANNEX I*)

Version 1.0, June 11, 2019

Sponsor of the clinical trial:

Georg-August-Universität Göttingen, Stiftung Öffentlichen Rechts,

Universitätsmedizin Göttingen, Vorstand

Coordinating investigator:

Prof. Dr. med. Norbert Schmitz

Author of the clinical study report:

Prof. Dr. med. Norbert Schmitz

Medizinische Klinik A, Domagkstrasse 3, 48149 Münster

Study start – End of study

First patient in: 23.03.2011 – End of study: 22.07.2017

1) Name of sponsor / company	Name: Rainer Bredenkamp Institut: Georg-August-Universität Göttingen, Stiftung Öffentlichen Rechts, Universitätsmedizin Göttingen, Vorstand Adresse: Robert-Koch-Straße 40, D-37075 Göttingen Tel.: +49 551/39-171347 Fax: +49 551/39-171344 E-Mail: sz-umg.sponsor-qm@med.uni-goettingen.de
2) Name of finished product	Not applicable (N/A)
3) Name of active substance	N/A
4) Individual Study Table	N/A
5) Title of study	Auto - vs. Allo -Transplantation in T-NHL (AATT) Autologous or allogeneic stem cell transplantation following conventional chemotherapy in younger patients (18-60 yrs.) with mature (peripheral) T-cell lymphoma DSHNHL 2006 1A Version 7.0 of March 1, 2010 Amendment 1 October 1, 2014
6) Coordinating investigator	Name: Prof. Dr. med. Norbert Schmitz Einrichtung: Medizinische Klinik A, Universitäts-Klinikum Münster Adresse: Domagkstrasse 3, 48149 Münster Tel.: 0251/8344830 Fax: 0251/8352673 E-Mail: Norbert.Schmitz@ukmuenster.de
7) Study centres	see appendix 01
8) Publication	Schmitz N et al. Allogeneic or autologous transplantation as first-line therapy for younger patients with peripheral T-cell lymphoma: Results of the interim analysis Annual Meeting of the American Society of Clinical Oncology (ASCO) 2015; 33(15): abstract 8507 Schmitz N et al. First-line therapy of T-cell lymphoma: Allogeneic or Autologous transplantation: Final Results of the AATT study Annual Meeting of the American Society of Clinical Oncology (ASCO) 2019; abstract 7503
9) Study period	First patient in: 23.03.2011 Last patient in: 22.07.2014 Randomization was stopped (25.06.2014) and the study was closed prematurely (end of recruitment 08.09.2014) after the data safety monitoring committee together with the coordinating investigator had decided that the probability of reaching the primary study endpoint (event-free survival after allogeneic transplantation 60% as compared to EFS after autologous transplantation 35%) was 10% or less.
10) Phase of development	Phase 3
11) Objectives	The aim of the AATT study was to investigate the following question in patients with untreated mature (peripheral) T-cell lymphoma by means of a prospective, randomized, multicenter clinical trial: Does primary allogeneic hematopoietic stem cell transplantation after conditioning with FBC (fludarabine, busulfan, cyclophosphamide) lead to a 25% improvement of event free survival after 3 years compared to autologous transplantation after high dose therapy with BEAM (BCNU, etoposide, cytarabine and melphalan)?

	Patients aged 18 to 60 years with newly diagnosed mature (peripheral) T-cell lymphoma were eligible for this trial. Patients with ALK-positive anaplastic large cell lymphoma (ALCL) and patients with stage I and aaIPI 0 were excluded. The primary endpoint was event-free survival (EFS). The primary objective was to show a difference in the 3-year EFS rate of 25%, with an error probability of 5% (two-sided), at a power of 80%.
12) Methodology	After diagnosis by the local pathologist eligible patients were randomized to either arm A (autologous transplantation) or arm B (allogeneic transplantation). In patients randomized to allogeneic transplantation HLA-typing of patient and siblings was initiated. An unrelated donor search was performed in patients without sibling donor. All randomized patients were to receive 4 courses of CHOEP-14 with formal restaging after course 4. Patients with CR, PR or no change proceeded to DHAP followed by collection of peripheral blood stem cells in patients randomized to autologous transplantation and in patients randomized to allogeneic transplantation but without donor. After 4 to 6 weeks patients were to proceed to transplantation: Patients randomized to autologous transplantation received high dose therapy (BCNU, etoposide, cytarabine, melphalan: BEAM) followed by transplantation of autologous PBSC. Patients randomized to allogeneic transplantation received myeloablative conditioning (fludarabine, busulfan, cyclophosphamide: FBC) followed by transplantation of allogeneic PBSC. GvHD prophylaxis included anti-thymocyte globuline (ATG), cyclosporine A, and mycophenolate mofetil. Patients randomized to allogeneic transplantation without donor received autologous PBSC. 140 patients with untreated mature peripheral T-cell lymphoma,age 18-60 years to be randomized to autologous or allogeneic transplantation (70 patients per arm) Intent-to-treat-analysis comparing treatment arms A and B by log-rank test for EFS and multivariate analyses adjusting for prognostic factors. Sequence of interventions according to protocol: pre-randomization evaluation, staging, checking eligibility and exclusion criteria, randomization, reference pathology,4 courses of CHOEP, re-staging,1 course of DHAP, high-dose therapy followed by transplantation of autologous or allogeneic stem cells, at least 2 years of follow up. Interim safety analysis as planned: DSMC voted to stop randomization on 25.06.2014
13) Number of patients	Patients (planned): 140 Patients actually randomized: 104 patients Patients treated and analyzed as per protocol: 103 patients (one patient without any study treatment excluded)
14) Diagnosis and main criteria for inclusion	1. Age: 18 to 60 years 2. Gender: Male and female patients to be included. 3. Risk group: Poor prognosis patients (patients with stage I **and** aaIPI 0 excluded) 4. Histology: • peripheral T-cell lymphoma, (PTCL) NOS • Lennert's lymphoma • T-zone lymphoma • T-immunoblastic variant • Perifollicular/Follicular variant

	• angioimmunoblastic T-cell lymphoma (AITL) • anaplastic large cell lymphoma, ALK negative • extranodal NK/T-cell lymphoma, nasal type • intestinal T-/NK-cell lymphoma (± enteropathy) • hepatosplenic gamma-delta lymphoma • subcutaneous panniculitis-like PTCL 5. Performance status: ECOG 0-3 (Karnofsky 40-100%) at time of randomization 6. Written informed consent 7. Declaration of participation by individual center
15) Test product	N/A
16) Duration of study	The duration of conventional chemotherapy for both treatment arms was 64 days followed by a 4-6 weeks rest period before transplantation. For patients receiving autologous transplantation duration of study treatment (Arm A) was 18-22 weeks, for patients receiving allogeneic transplantation (Arm B) 20-26 weeks, respectively. In case of serious complications treatment duration could be longer in both treatment arms
17) Reference therapy, dose and mode of administration	This study compared modalities (autologous and allogeneic transplantation) rather than drugs. Conventional therapy (CHOEP/ DHAP) followed by autologous transplantation served as a reference because results from prospective trials studying this treatment algorithm were available before start of study. (Details of the reference arm and the experimental arm including allogeneic transplantation see attachment.)
18) Criteria for evaluation: Efficacy, Safety	<u>Efficacy:</u> - Thirty-six of 103 patients (35%) (20 patients randomized to autologous and 16 patients randomized to allogeneic transplantation) did not complete study treatment mostly due to early progression (29 patients: 28% of all treated patients). Other reasons for early termination were: diagnosis not PTCL (n=4), toxicity (n=1), patient decision (n=1), mobilization failure (n=1), other (n=1). Only 67 patients (65%) could be treated as per protocol (34 patients in the autologous treatment arm, 33 patients in the allogeneic treatment arm). Of 33 patients in the allogeneic treatment arm, however, 26 patients only had an allogeneic transplantation. Seven patients received an autologous transplant because no donor became available (6 patients) during the time period stipulated by the protocol; one patient was autografted after the allogeneic treatment arm had been closed. Thus, 41 patients had an autologous and 26 patients had an allogeneic transplant. In patients receiving 4 courses of CHOEP and 1 course of DHAP protocol adherence was generally high (see appendix 02). - In the FAS-population 46 (45%) patients achieved a complete response (CR) or CRu (21 patients or 39% randomized to autologous transplantation and 25 patients or 51% randomized to allogeneic transplantation). The overall response rate (CR/ CRu/ PR) was 56% for patients randomized to autologous and 57% for patients randomized to allogeneic transplantation. 35% of patients in the autologous treatment arm and 33% in the allogeneic arm showed progressive disease (PD) at the end of study treatment. Relapse rates for patients with CR/ CRu at the end of therapy were 33% for patients randomized to autologous and 12% for patients randomized to allogeneic transplantation. EFS, PFS, and OS at 3 years were 38%, 39%, and 70% for patients randomized to autologous transplantation and 43%, 43%, and 57% randomized to allogeneic transplantation. None of these results were significantly different. The respective Kaplan-Meier plots are

shown in the appendix 3. Patients with age-adjusted IPI (aaIPI) 0 or 1 did significantly better than patients with aaIPI 2 or 3 (appendix 4) overall and in both treatment arms.

- 67 patients completed the study as per protocol. Seven patients randomized to allogeneic transplantation were autografted because no fully matched donor could be found in the time (4-6 weeks) stipulated per protocol. Finally, 60 patients formed PPS2.
- Analyses of FAS, PPS1, PPS2, PPS3, PPS4, and PPS5 regarding primary and secondary endpoints did not change the major conclusion of the trial: no significant outcome differences between patients randomized to autologous and allogeneic transplantation as well as between patients actually transplanted.
- A planned safety interim analysis was performed in June 2014 after 58 patients were analyzable. Upon analysis of all available data, the data safety monitoring committee (DSMC) and the principal investigator (PI) decided to stop the study because the probability to meet the primary endpoint was calculated to be 10% or less. Randomization of patients was stopped in June 2014, and the study was stopped overall in September 2014.The results of the interim analysis were presented at the Annual Meeting of the American Society of Clinical Oncology 2015 (J Clin Oncol 2015,suppl.,abstract 8507). Results of the interim and the final analysis did not differ substantially. In particular, as predicted, differences in EFS, PFS, and OS could not be demonstrated.

<u>Safety:</u>

Hematological toxicity (anemia, leukocytopenia, thrombocytopenia), grades 3-5, was expected and moderately frequent after CHOEP and DHAP (appendix 5) triggering red blood cell transfusions in 23%, platelet transfusions in 6%, and administration of interventional antibiotic therapy in 30% of all CHOEP cycles although the majority of patients received prophylactic G-CSF, antibacterials, antifungal and antiviral medication. Non-hematological adverse events observed with CHOEP therapy per cycle, during all cycles, and per patient were of low frequency and mostly mild to moderate (for summary of adverse events CTC grades 3-5 see appendix 6). Infections CTC 3-5 occurred in 9% of all patients after CHOEP and were mostly of bacterial origin (appendix7). Hematological and non-hematological toxicities after DHAP were expected; infections CTC grade 3-5 occurred in 4% of cases (for details see appendix 8). Differences between treatment arms were not expected (all patients were to receive 4 cycles of CHOEP and 1 cycle of DHAP) and did not occur.

Patients undergoing autologous transplantation experienced diarrhea CTC grades 3-5 (10% of patients), mucositis (32%), and infection (32%) as most frequent non-hematological toxicities. Patients undergoing allogeneic transplantation experienced diarrhea (12%), renal toxicity (15%), mucositis (23%), and infection (38%) as most frequent adverse events CTC grades 3-5. Hematological toxicity was expected and universal both after autologous and allogeneic transplantation. For more details see appendix 9.

The causes of death after autologous and allogeneic transplantation are summarized in slide 446. Seven patients (78%) receiving autologous SCT but only one patient (11%) receiving allogeneic SCT died from lymphoma. In contrast, treatment-related mortality (TRM) was observed in eight patients (89%) after allogeneic and in one patient (11%) (no study treatment) after autologous transplantation. The specific causes of death for patients who had undergone allogeneic transplantation are summarized in appendix 10. Five patients were reported to have died from acute (n=3) or chronic (n=2) graft-vs.-host disease (GvHD).The

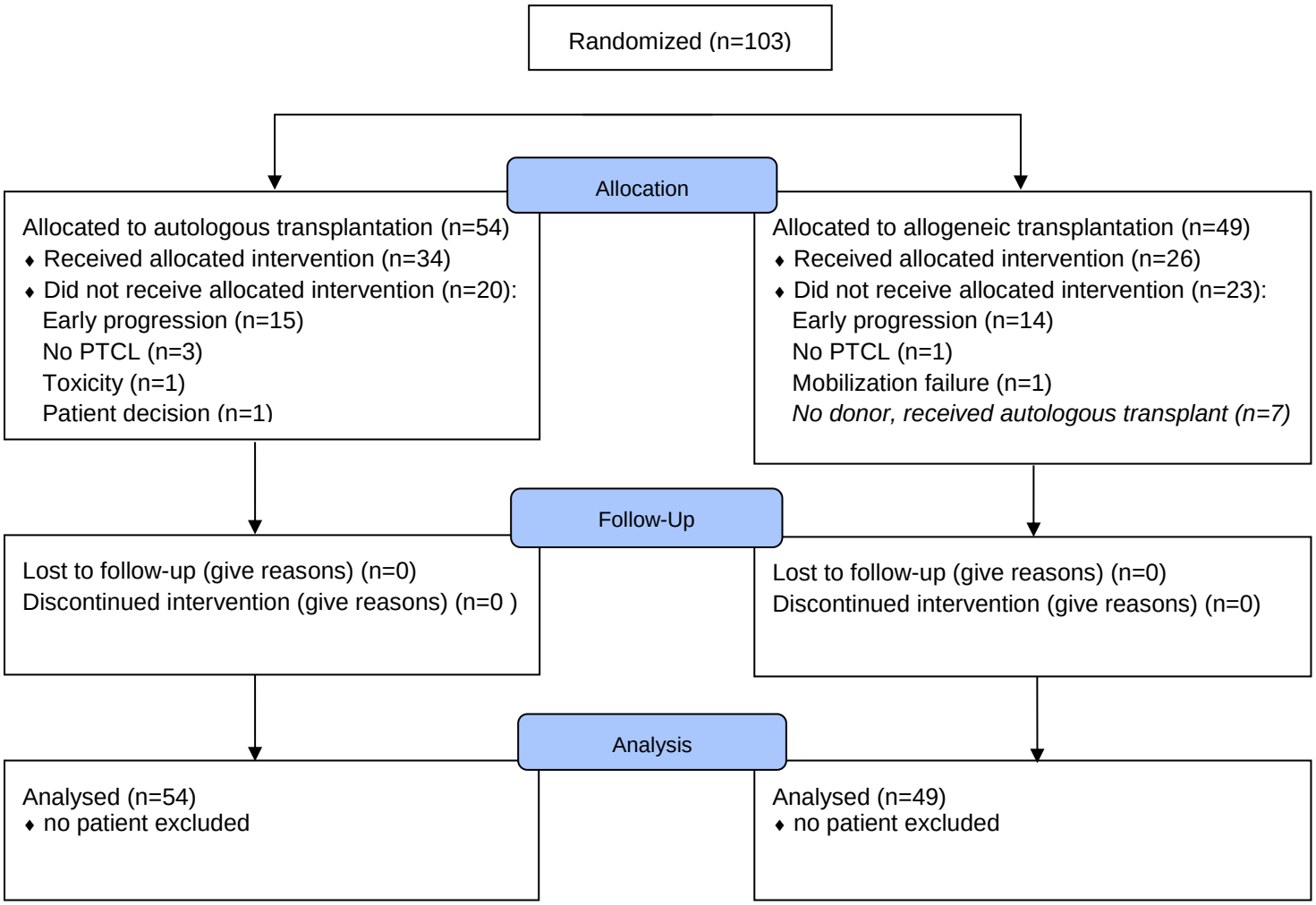
	other causes of death (CMV infection, varicella encephalitis, infection of unknown origin) are well-known complications of posttransplant cytopenias and immunosuppression or occurred in the context of profound and persisting immunosuppression after allogeneic transplantation (hepatic failure due to EBV-associated B-cell lymphoma). One patient died from secondary neoplasia after autologous transplantation. All patients undergoing transplantation were in hospital as were 38%-78% of patients undergoing CHOEP therapy. All patients undergoing DHAP were hospitalized because G-CSF was administered after chemotherapy in order to collect hematopoietic stem cells. The spectrum of PTCL entities observed in the trial corresponds to our expectations with AITL patients being most frequent followed by PTCL NOS, and ALCL, ALK-negative. This order of PTCL frequencies matches a recent publication from France. Histological subtypes were evenly distributed between treatment arms .Reference pathology was available in all but 3 patients. Eight patients (8%) could not finally be classified as PTCL. This percentage is within limits expected. In summary, the sequential treatment with 4 courses of CHOEP, one course of DHAP, BEAM high-dose chemotherapy and autologous transplantation was characterized by expected mild to moderate toxicities but was safe (one TRM occurred); however, patients relapsed before transplantation and continued to relapse also after high-dose therapy. The shape of the survival curves for this group of patients documents that relapses did occur also between 2 and 3 years after autologous transplantation and raises concern that further relapses may occur later in the course of disease. In contrast, only one patient who actually underwent allogeneic transplantation relapsed; the survival curves for patients after allogeneic transplantation suggest that the risk of relapse for such patients is very low. Unfortunately, 7 (27%) of all patients actually receiving an allotransplant died from GvHD or infectious complications associated with GvHD and/ or immunosuppression caused by the transplant procedure itself or immunosuppressive medication necessary to prevent GvHD. Because the excess of TRM seen after allogeneic transplantation in this and other studies we do not recommend to integrate allogeneic transplantation into the treatment algorithm of patients with newly diagnosed PTCL.
19) Statistical methods	Statistical analysis was performed according to the Statistical Analysis Plan (SAP) Version 2.0 of the trial. The SAP corresponded to the initial statistical analysis plan of the trial (Version 1.0) for the interim analysis.protocol version. The following populations were analyzed: **Full analysis set (FAS):** all randomized patients with study treatment 103 patients • 54 patients randomized to autologous transplantation • 49 patients randomized to allogeneic transplantation **Per protocol set 1 (PPS1):** all patients from FAS fulfilling inclusion criteria and reference pathology according to protocol 87 patients • 46 patients randomized to autologous transplantation • 41 patients randomized to allogeneic transplantation **Per protocol set 2 (PPS2):** all randomized patients who were transplanted according to the randomized type of SCT

	60 patients • 34 patients randomized to autologous transplantation • 26 patients randomized to allogeneic transplantation **Per protocol set 3 (PPS3):** represents all patients from PPS2 fulfilling all inclusion criteria and reference pathology rendered 55 patients • 31 patients randomized to autologous transplantation • 24 patients randomized to allogeneic transplantation **Per protocol set 4 (PPS4):** represents all randomized and transplanted patients analyzed according to the transplant actually received (autologous or allogeneic). 67 patients • 41 patients receiving autologous transplantation • 26 patients receiving allogeneic transplantation **Per protocol set 5 (PPS5):** Represents all patients from PPS4 fulfilling inclusion criteria and with reference pathology according to protocol 62 patients • 46 patients receiving autologous transplantation • 41 patients receiving allogeneic transplantation Whenever possible results from the FAS population are given in this report. Comparisons of patient subgroups are made in order to better demonstrate results of transplantation according to randomization (PPS2) or according to the type of transplant actually received (PPS4). SAE's and deaths occurring during the study were continuously monitored by the coordinating investigator within the annual safety report. The first safety, and toxicity and outcome analysis was done after 58 patients had been treated. Conditional power calculation was done. The trial was terminated after data were made available, discussed within the data safety and monitoring committee (DSMC), and a decision to stop the study was made. Reasons for termination of the trial were the low probability to meet the primary endpoint (and demonstrate the superiority of allogeneic over autologous transplantation). Because only 103 patients started treatment the statistical power for detecting the planned 25% difference for the primary endpoint 3-years EFS was about 70%.
20) Summary - Conclusions	Between March 2011 and July 2014, 103 younger patients (age 24-60 years, median 50 years) with PTCL from 44 centers in France (60 patients) and Germany (44 patients), (for details see slides 7-9), were randomized to receive 4 x CHOEP, 1 x DHAP, followed by high-dose therapy and autologous stem cell transplantation (arm A) or myeloablative conditioning with Fludarabine, Busulfan, and Cyclophosphamide (FBC regimen) and transplantation of allogeneic stem cells (arm B). Of the full analysis set (FAS-population) one third of patients (n=36 patients) were unable to proceed to autologous or allogeneic transplantation mostly because of early progression (n=28). Sixty-seven patients (65%) were transplanted albeit 7 patients randomized to allogeneic transplantation had to receive an autologous transplant because a matched donor was unavailable. Finally, 60 patients were transplanted as randomized (34 autologous and 26 allogeneic transplants). Overall, sixty-seven patients were transplanted with 7 more patients receiving an autologous graft because no allogeneic donor had been found.

	Thirteen patients randomized to autologous transplantation and 11 patients randomized to allogeneic transplantation died of lymphoma. Treatment-related mortality from study treatment only was 0% in the autologous, and 16% in the allogeneic treatment arm. Considering study and salvage therapy, 4 patients (7%) in the autologous treatment arm and 10 patients (20%) in the allogeneic treatment arm died of TRM. Including one patient dying from secondary neoplasia in the autologous treatment arm, 18 patients (33%) randomized to autologous transplantation and 21 patients (43%) randomized to allogeneic transplantation have died. The EFS, PFS, and OS of patients in the FAS population did not significantly differ. Analysis of the PPS4 (only patients who actually received the type of transplant they had been randomized to) also showed no significant differences in EFS, PFS, or OS; however, the causes of death after transplantation were very much different. While patients receiving an autograft experienced no TRM but suffered 7 lymphoma deaths (with the survival curves suggesting an ongoing relapse risk during years 2-3 after transplantation) patients who had an allogeneic transplantation experienced only 1 lymphoma death; however, 8/ 26 patients (31%) died of complications typically observed after allogeneic transplantation. Because of its imminent risks and high TRM, in particular, allogeneic transplantation cannot be generally recommended for consolidation of first-line therapy in patients with PTCL. Rather, patients should be monitored by PET scan or other sensitive methods for early progression which would make such patients immediate candidates for allogeneic transplantation because up to now no other treatment has shown the potential of bringing significant numbers of relapsed and refractory patients into long-term remission. In order to improve outcomes for patients with PTCL, first-line therapy still consisting of CHO(E)P must be improved in order to reduce early progression and relapse. New drugs (brentuximab vedotin, romidepsin, azacytidine) given in combination with chemotherapy may serve to achieve this goal. With the success of haplo-identical transplantation in lymphoma the problem to find a suitable donor in a short period of time has solved. If results with haplo-identical transplants or allogeneic transplantation after non-myeloablative conditioning can avoid the high TRM seen in this study while preserving the vigorous graft-vs.lymphoma effect obviously exerted by the allogeneic graft remains to be settled.
21) Date of report	June 11, 2019

CONSORT 2010 Flow Diagram

(http://www.consort-statement.org/ - Download: 09.04.2018)



Appendix 1 Overview of sites

Site No	Site
232	Ev. Diakonie Krankenhaus Bremen Medizinische Klinik II, Gröpelinger Heerstr. 406/408, 28239 Bremen
141	Klinikum Chemnitz Klinik für Innere Medizin III, Bürgerstr. 2, 09113 Chemnitz
289	Universitätsklinikum Carl Gustav Carus Dresden Meizinische Klinik und Poliklinik I, Fetscherstr.74, 01307 Dresden
53	Kliniken Essen-Süd, Ev. KH Essen Werden Zentrum für Innere Medizin, Hämatologie, Onkologie und Stammzelltransplantation, Pattbergstr. 1-3, 45239 Essen-Werden
545	Universitätsklinkum Essen Hämatologie und Intern. Onkologie, Klinik für Knochenmarktransplantation, Hufelandstr. 55, 45122 Essen
61	Georg-August-Universität Göttingen Abteilung Hämatologie und Onkologie, Robert-Koch-Str. 40, 37075 Götingen
106	Kath. Krankenhaus Hagen, St. Marien Hospital Klinik für Hämatologie und Onkologie, Bergstr. 56, 58095 Hagen
401	Asklepios Klinik St. Georg Abteilung Hämatologie, Onkologie und Stammzelltransplantation, Lohmühlenstr. 5, 20099 Hamburg
70	Universitätsklinik Heidelberg Medizinische Klinik V, Im Neuenheimer Feld 410, 69120 Heidelberg
113	Universitätsklinikum des Saarlandes Innere Medizin I, -Onkologie, Hämatologie, klein. Immunologie und Rheumatologie-, Kirrberger Str. 1, 66421 Homburg
59	Städtisches Klinikum Karlsruhe II. Medizinische Klinik, -Hämatologie, Onkologie, Palliativmedizin, Infektionskrankheiten-, Moltkestr. 90, 76133 Karlsruhe

Site No	Site
602	CHU ESTAING Hématologie clinique adultes et thérapie cellulaire 1 place Lucie Aubrac 63000 CLERMONT FERRAND Cedex1
713	CENTRE HOSPITALIER SUD FRANCILIEN Hôpital Gilles de Corbeil 59 bd Henri Dunant 91100 CORBEIL-ESSONNES
586	UNITE HEMOPATHIE LYMPHOIDE Hôpital Henri Mondor 51 avenue du Maréchal de Lattre de Tassigny 94010 CRETEIL
587	CHU - HOPITAL ENFANTS Hématologie clinique 2 bd Maréchal de Lattre de Tassigny 21000 DIJON
603	HOPITAL MICHALLON Hématologie clinique BP 217 38043 GRENOBLE Cedex 09
604	CENTRE HOSPITALIER DEPARTEMENTAL Méd. Interne-Hématologie Boulevard S. Moreau Les Oudairies 85925 LA ROCHE SUR YON Cedex 9
714	CENTRE HOSPITALIER Département d'oncologie médicale Reilly I 194 avenue Rubillard 72037 LE MANS Cedex 1
715	CHU DUPUYTREN Sce d'hématologie clinique et de thérapie cellulaire 2 Avenue Martin Luther King 87042 Limoges Cedex
606	HOPITAL SAINT-ELOI Sce d'hématologie clinique 80 Avenue Augustin Fliche 34295 Montpellier Cedex 5
717	CENTRE HOSPITALIER DE MULHOUSE Sce d'hématologie 20 Avenue du Dr Laennec 68100 Mulhouse
608	CENTRE CATHERINE DE SIENNE Hématologie clinique 2 rue Eric TABARLY 44200 NANTES

355	Universitätsmedizin der Johannes-Gutenberg-Universität Mainz III. Medizinische Klinik und Poliklinik, Langenbeckstr. 1 - Geb. 302, 55131 Mainz
23	Universitätsklinikum Mannheim III. Medizinische Klinik Mannheim, Pettenkoferstr. 22, 68169 Mannheim
12	Universitätsklinikum Gießen und Marburg Klinik für Innere Medizin, SP Hämatologie, Onkologie und Immunologie, Baldingerstrasse, 35033 Marburg
145	Kliniken Maria Hilf, KH St. Franziskus Klinik für Hämatologie, Onkologie und Gastroenterologie, Viersener Str. 450, 41063 Mönchengladbach
337	Klinikum der Universität München-Großhadern Medizinische Klinik III, Marchioninistr. 15, 81377 München
372	Klinikum rechts der Isar der Technischen Universität München III. Medizinsiche Klink, Ismaninger Str. 22, 81675 München
137	Klinikum Nürnberg Nord 5. Medizinische Klinik, Prof.-Ernst-Nathan-Str. 1, 90419 Nürnberg
230	Klinikum Oldenburg Abteilung Onkologie und Hämatologie, Dr.-Eden-Str. 10, 26133 Oldenburg
17	Universitätsklinikum Ulm Klinik für innere Medizin III, Albert-Einstein-Allee 23, 89081 Ulm
704	CHU SERVICE DES MALADIES DU SANG 4 rue Larrey 49033 ANGERS cedex 01
598	HOPITAL HENRI DUFFAUT Onco-hématologie 305 rue Raoul FOLLEREAU 84902 AVIGNON CEDEX 9
707	CENTRE HOSPITALIER DE LA COTE BASQUE Hématologie 13 Avenue de l'Interne Jacques Loeb 64109 BAYONNE
607	CHU - HOTEL DIEU Hématologie clinique 1 Place Alexis Ricordeau BP 1005 44093 NANTES Cedex 01
718	HOPITAL ARCHET 1 Hématologie Clinique 151 route de St Antoine de Ginestière BP 3079 06202 NICE cedex 3
719	CHU NIMES Unité Onco-Hématologie Groupe Hospitalo-Universitaire Caremeau Place du Pr Debré 30029 NIMES
609	HOPITAL DE LA SOURCE Oncologie médicale 14 Avenue de l'Hôpital BP 86709 45067 ORLEANS Cedex 02
610	HOPITAL COCHIN Unité d'Hématologie 27 rue du Faubourg St Jacques 75679 PARIS Cedex 14
591	HOPITAL SAINT-ANTOINE Hématologie 184 rue du faubourg Saint-Antoine 75571 PARIS Cedex 12
592	HOPITAL NECKER – ENFANTS MALADES Sce d'hématologie clinique adultes 149 rue de Sèvres 75743 PARIS Cedex 15
593	HOPITAL LA PITIE SALPETRIERE Hématologie 83 bd de l'Hôpital, 75651 Paris Cedex
594	HOPITAL SAINT LOUIS Hématologie 1 Ave Claude Vellefaux 75475 Paris
595	CHG SAINT JEAN Hématologie 20 avenue du Languedoc BP 4052 66046 PERPIGNAN Cedex
583	HOPITAL ROBERT DEBRE Sce d'hématologie clinique U43 Avenue du Général Koenig 51092 REIMS
720	HOPITAL PONTCHAILLOU Hématologie clinique 2 avenue Henri Le Guilloux 35033 RENNES Cedex 9

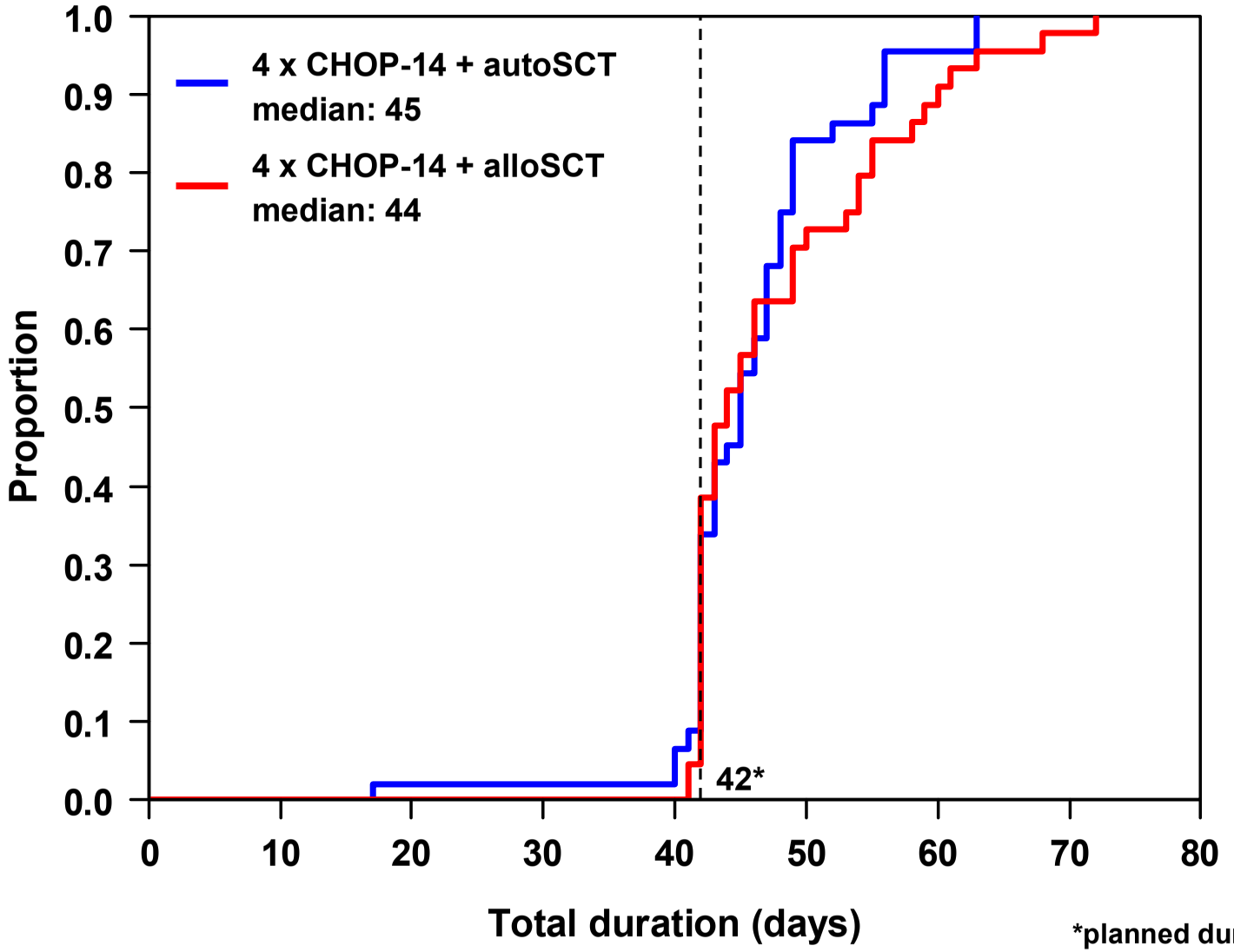
708	HÔPITAL MINJOZ Hématologie 2 boulevard Fleming 25030 BESANçON Cedex
709	CENTRE HOSPITALIER Hématologie-Oncologie 2 Rue Valentin Haüy BP 740 34525 BEZIERS Cedex
601	GROUP HOSPITALIER SUD HOPITAL HAUT LEVEQUE Maladies du Sang 1 avenue Magellan 33604 PESSAC
584	POLYCLINIQUE BORDEAUX NORD AQUITAINE Service de radiothérapie oncologie 15 rue Claude Boucher 33300 BORDEAUX CEDEX
712	HOPITAL MORVAN Service d'hématologie 5 avenue Foch 29609 BREST Cedex
585	SERVICE D'HEMATOLOGIE CLINIQUE CHR Clémenceau Avenue Georges Clémenceau 14 000 CAEN
721	CENTRE RENE HUGUENIN Hématologie 35 rue Dailly 92212 SAINT CLOUD
613	INSTITUT CANCEROLOGIE DE LA LOIRE (ICL) Hématologie 108 bis Avenue Albert Raimond 42270 SAINT PRIEST-EN-JAREZ Cedex
722	HOPITAUX UNIVERSITAIRES DE STRASBOURG Département d'hématologie et d'oncologie CHRU Hautepierre 67098 STRASBOURG cedex
723	HOPITAL PURPAN Attachée de Recherche Clinique Service d'Hématologie IUC ONCOPOLE 1 avenue Irène Joliot Curie 31100 Toulouse cedex 9
612	HOPITAL BRETONNEAU Service d'Hématologie 2 boulevard Tonnellé 37044 TOURS Cedex 9
589	CHU DE BRABOIS Hématologie - Médecine interne Rue du Morvan 54400 VANDOEUVRE-LES-NANCY

Appendix 2

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=58)

Total duration of 4xCHOEP-14



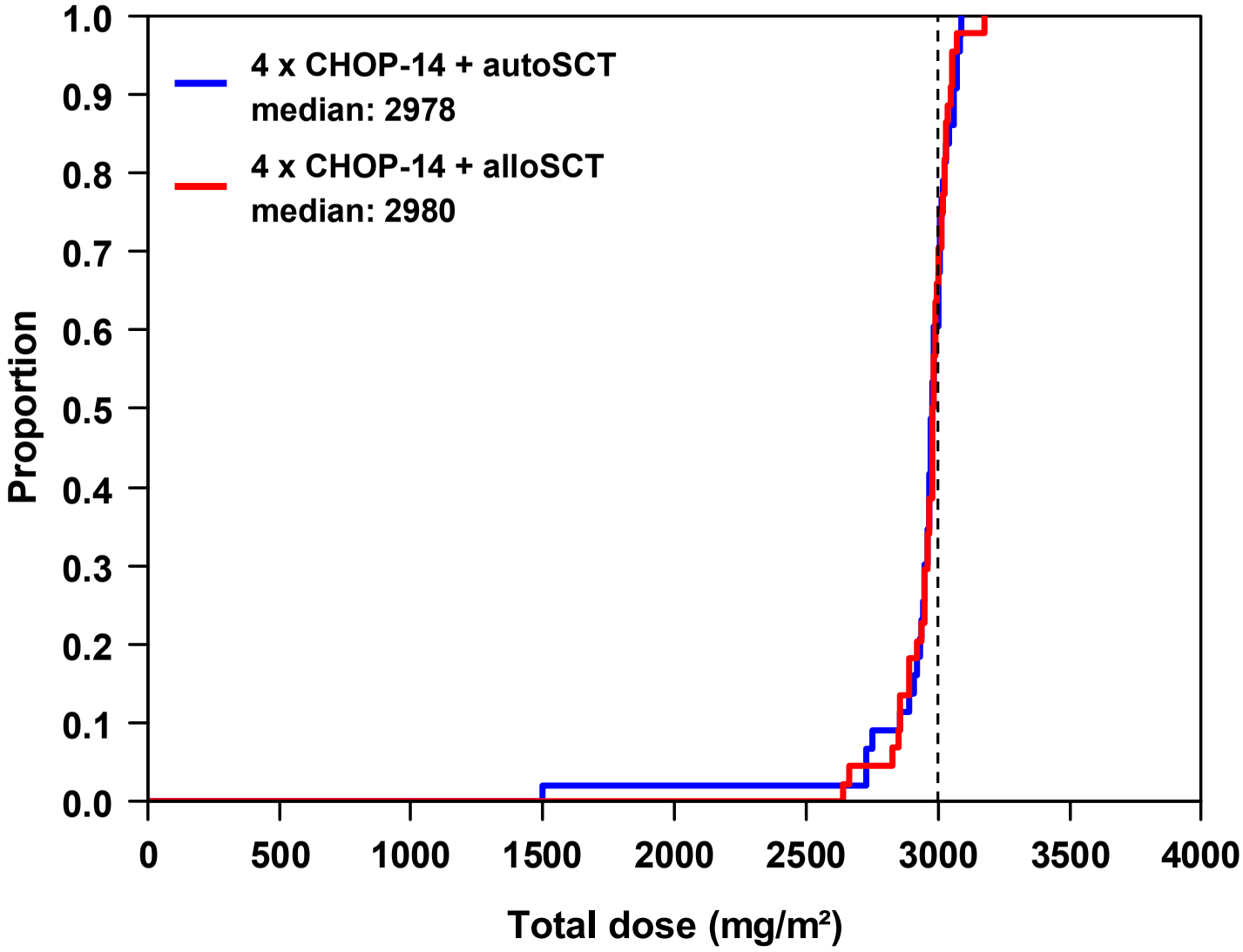
DSHNHL 27.11.18

*planned duration for 3 courses
only patients with at least two cycles are included

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Absolute dose of Cyclophosphamide



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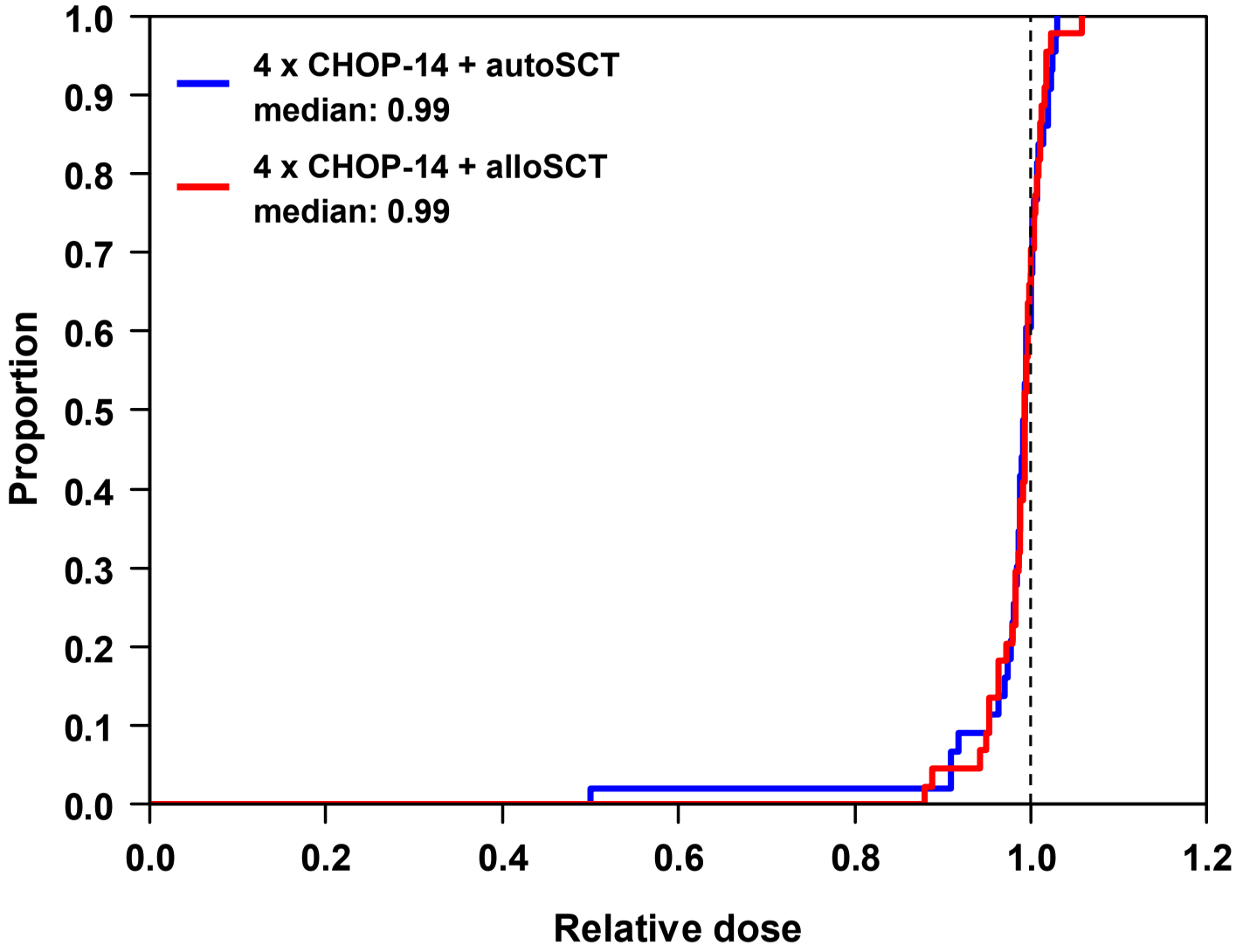
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Relative dose of Cyclophosphamide



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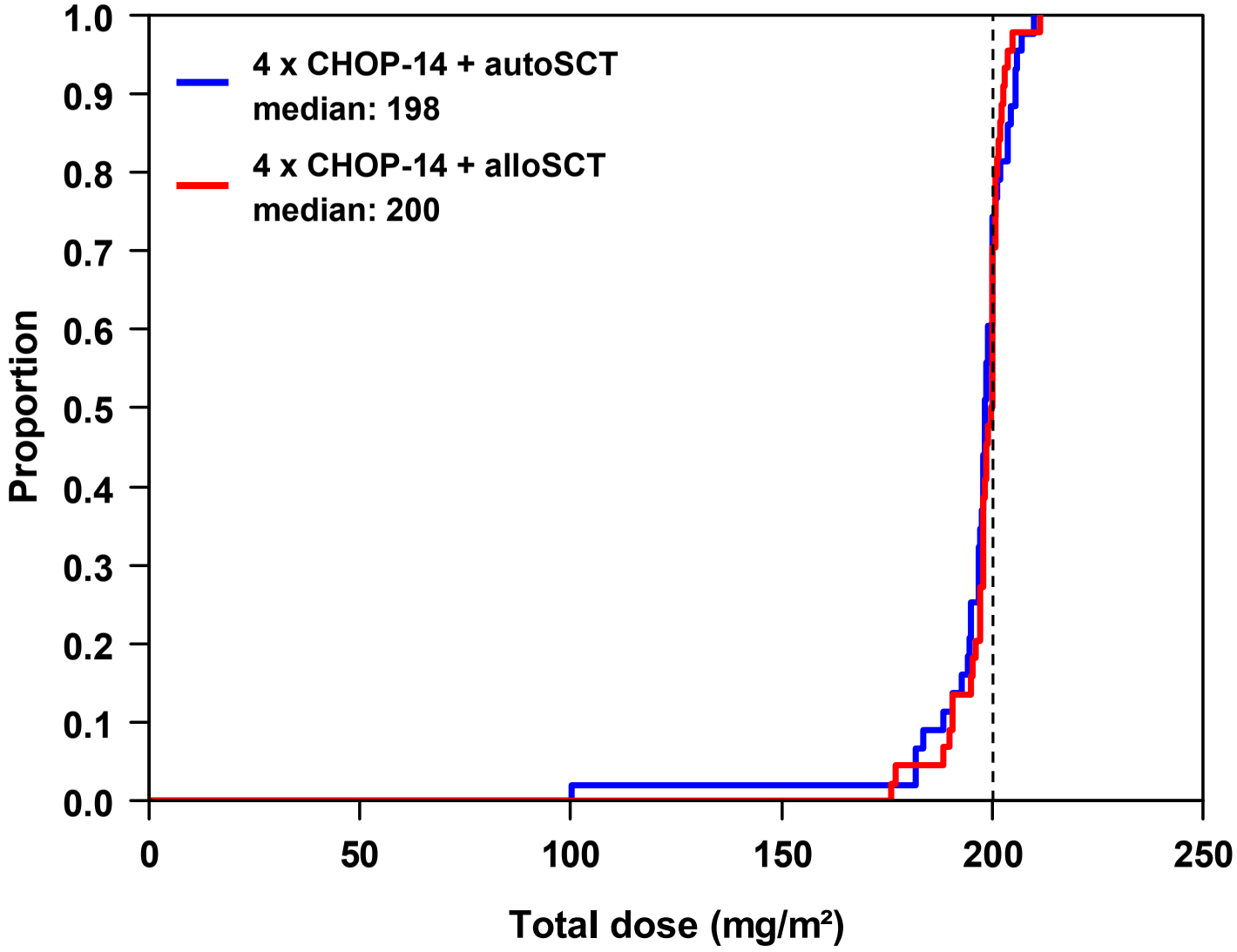
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Absolute dose of Doxorubicin

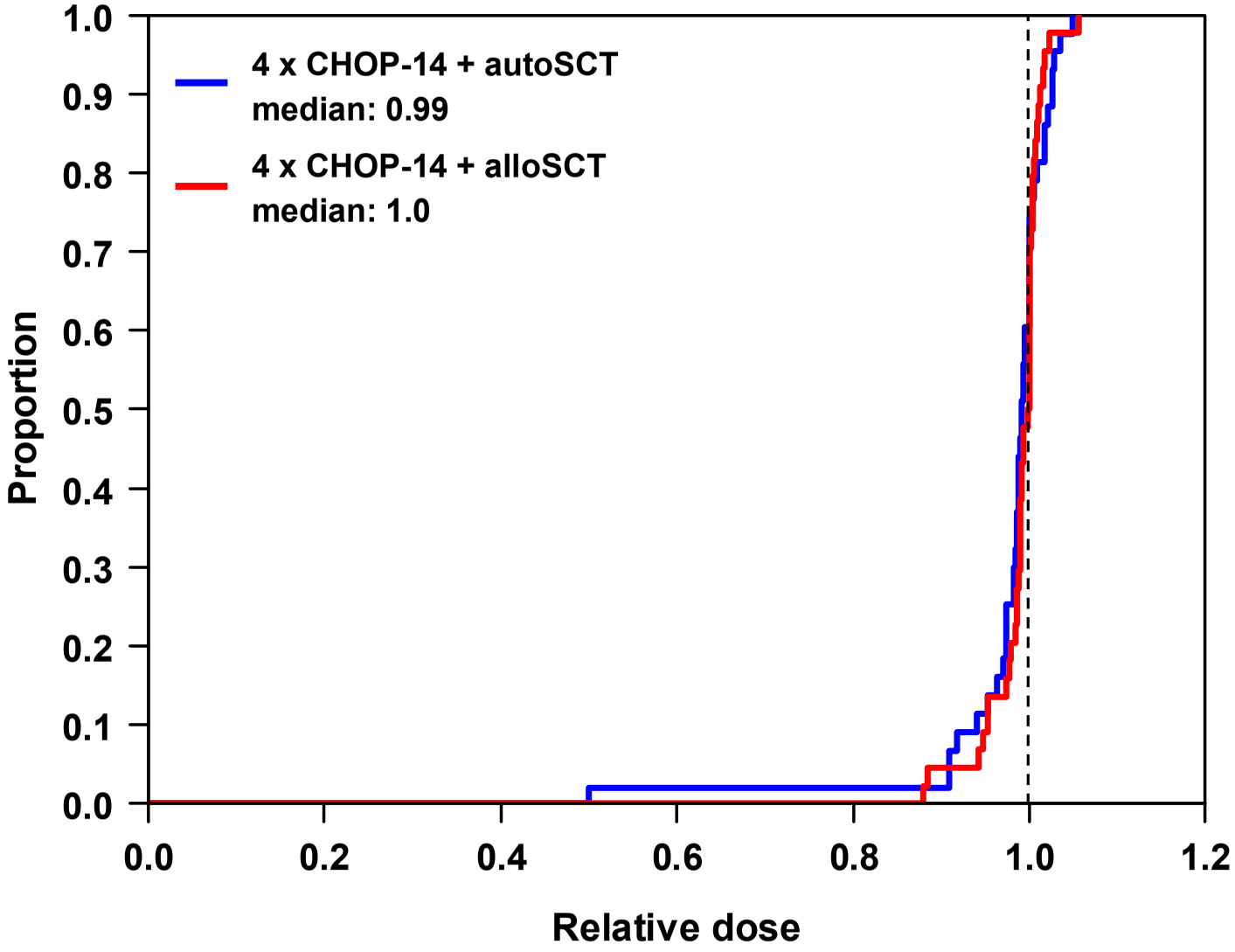


DSHNHL 27.11.18

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Relative dose of Doxorubicin



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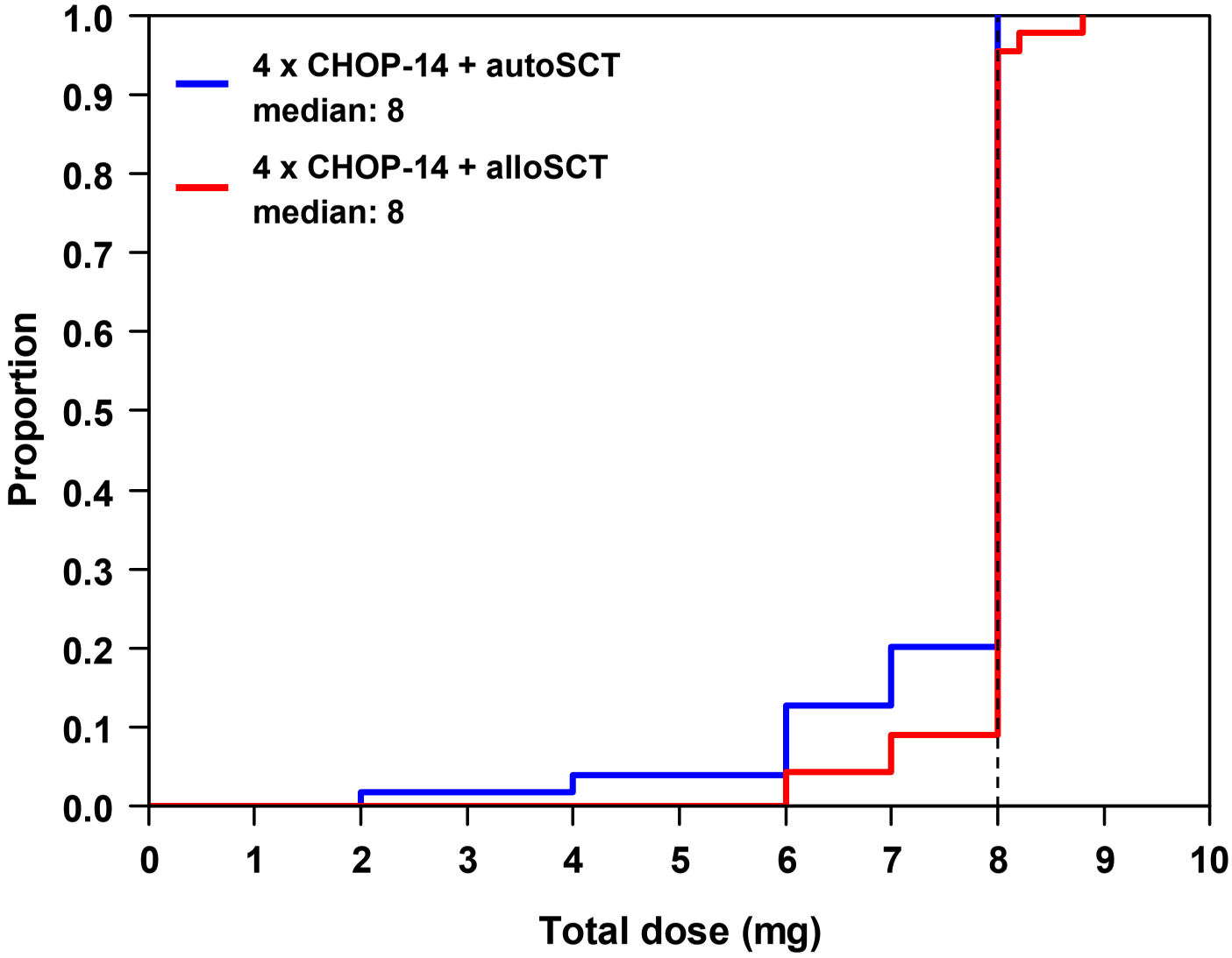
Patients 18 - 60 years, T-cell, FAS (n=103)

Absolute dose of Vincristine



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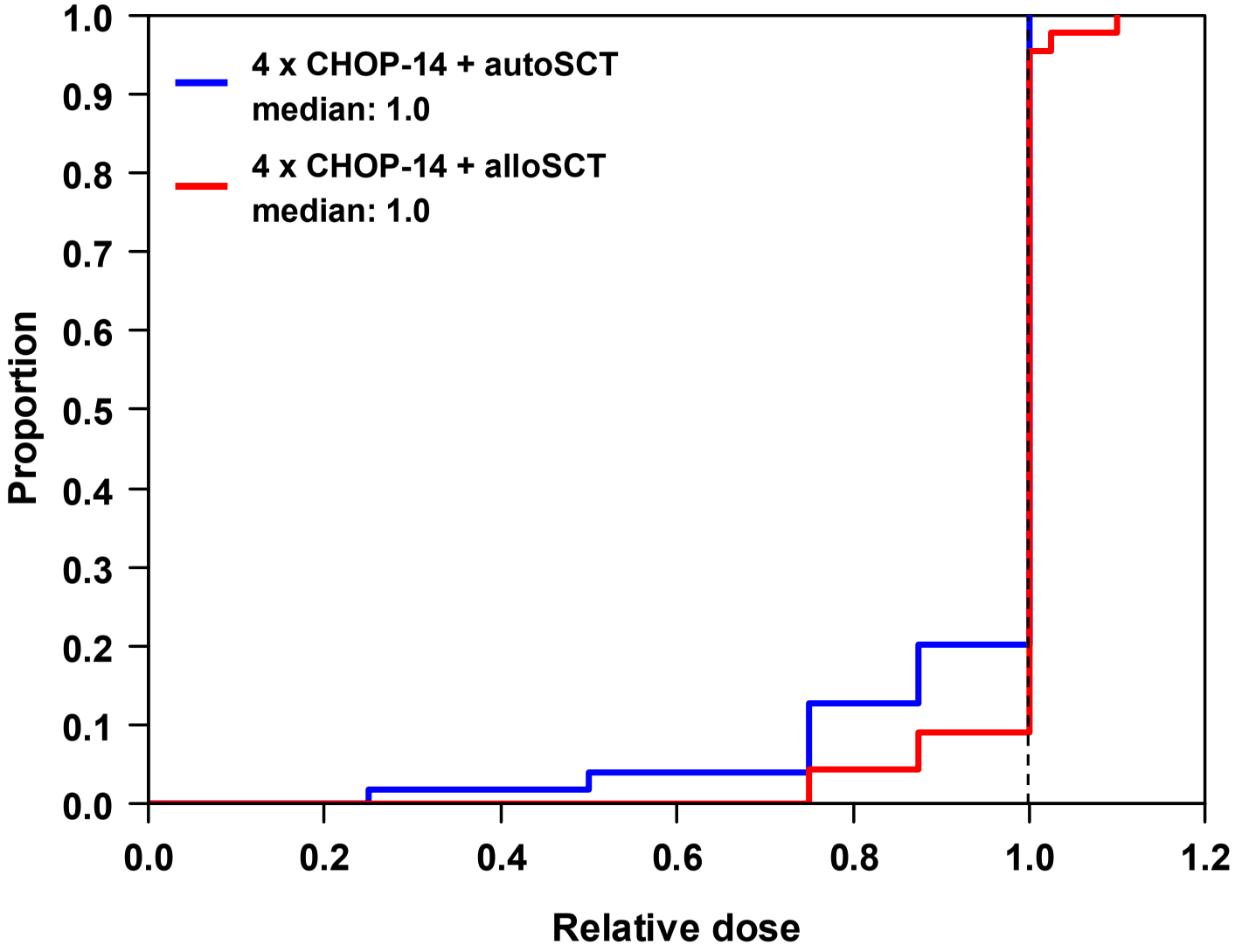
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Relative dose of Vincristine



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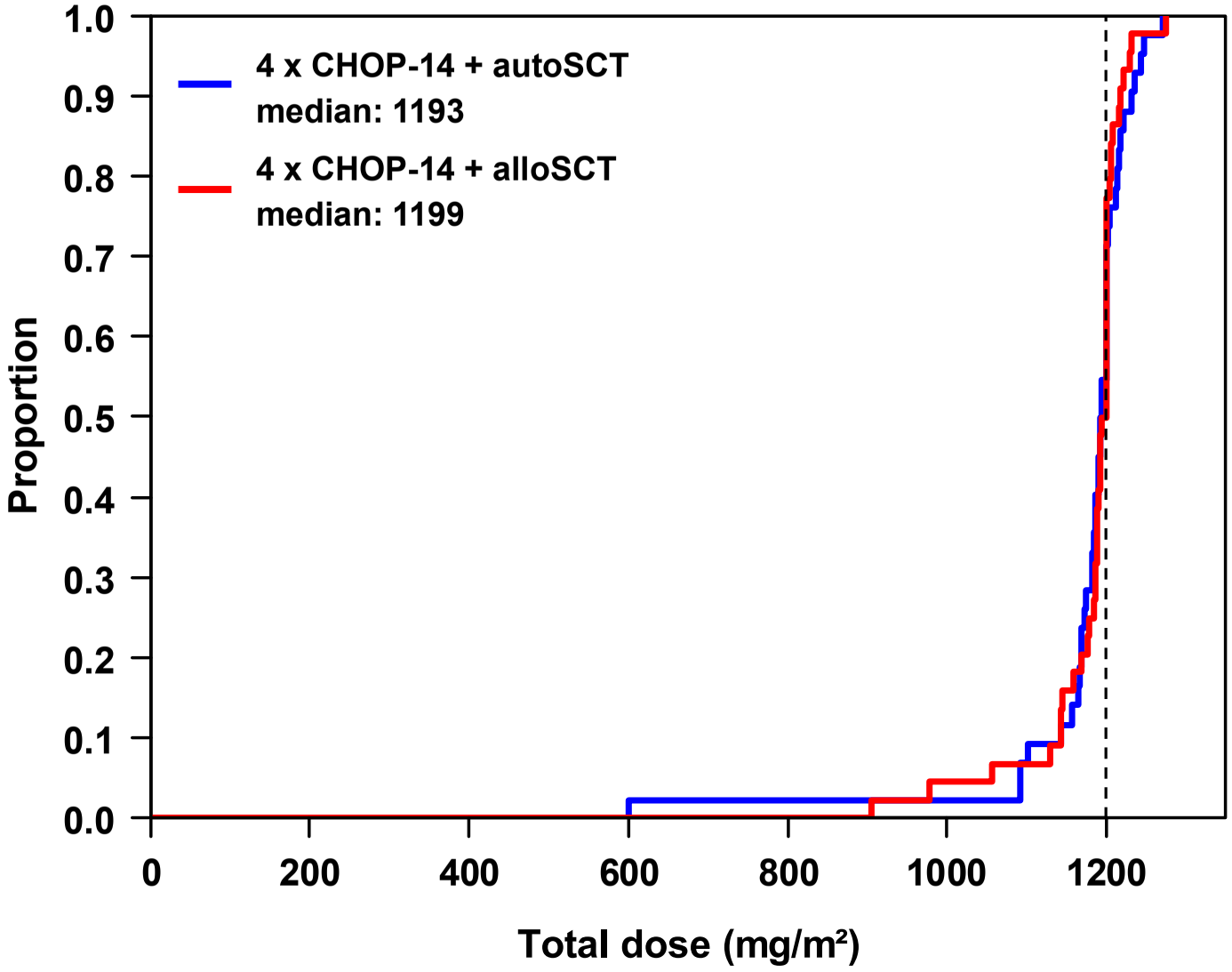
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Absolute dose of Etoposide



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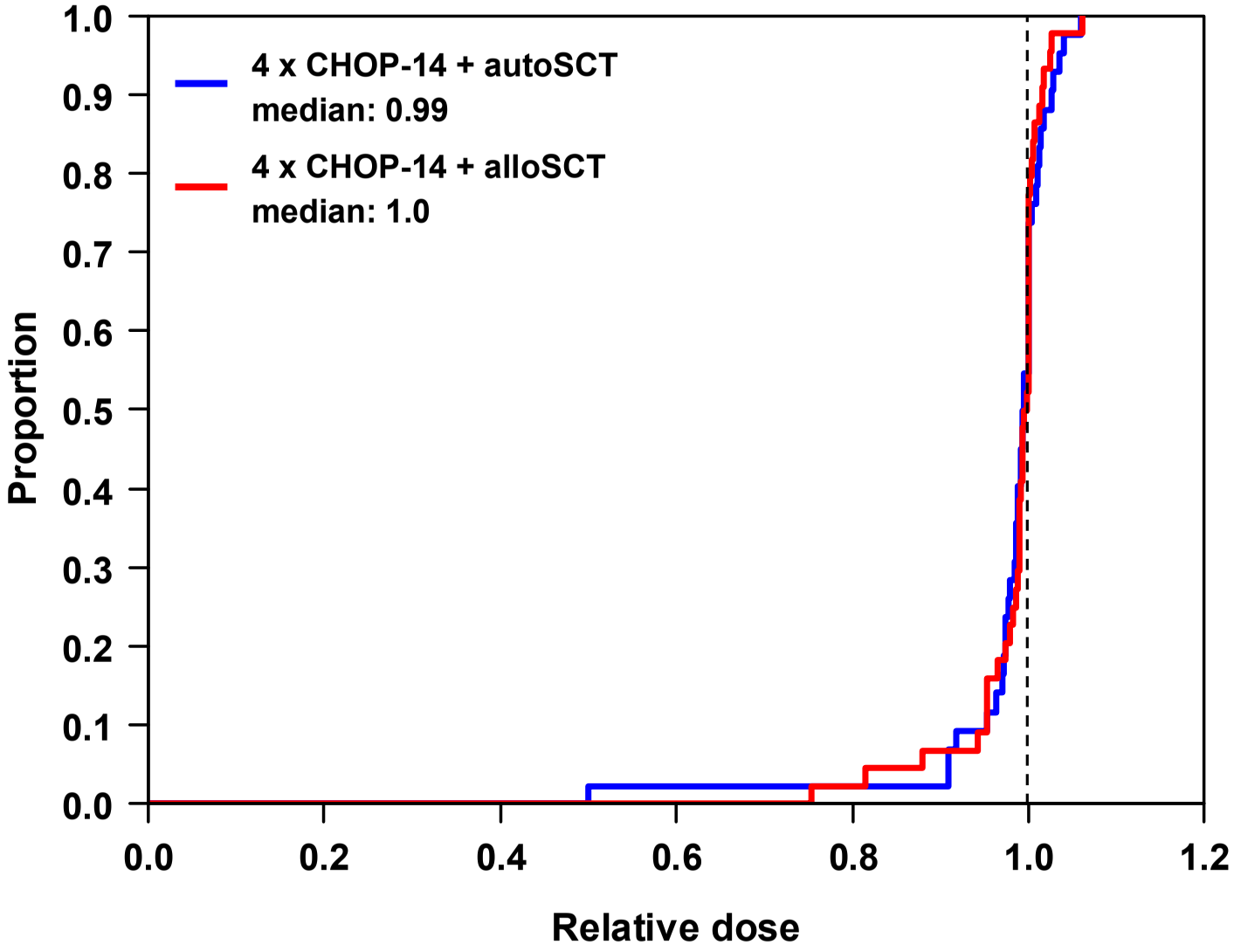
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Relative dose of Etoposide



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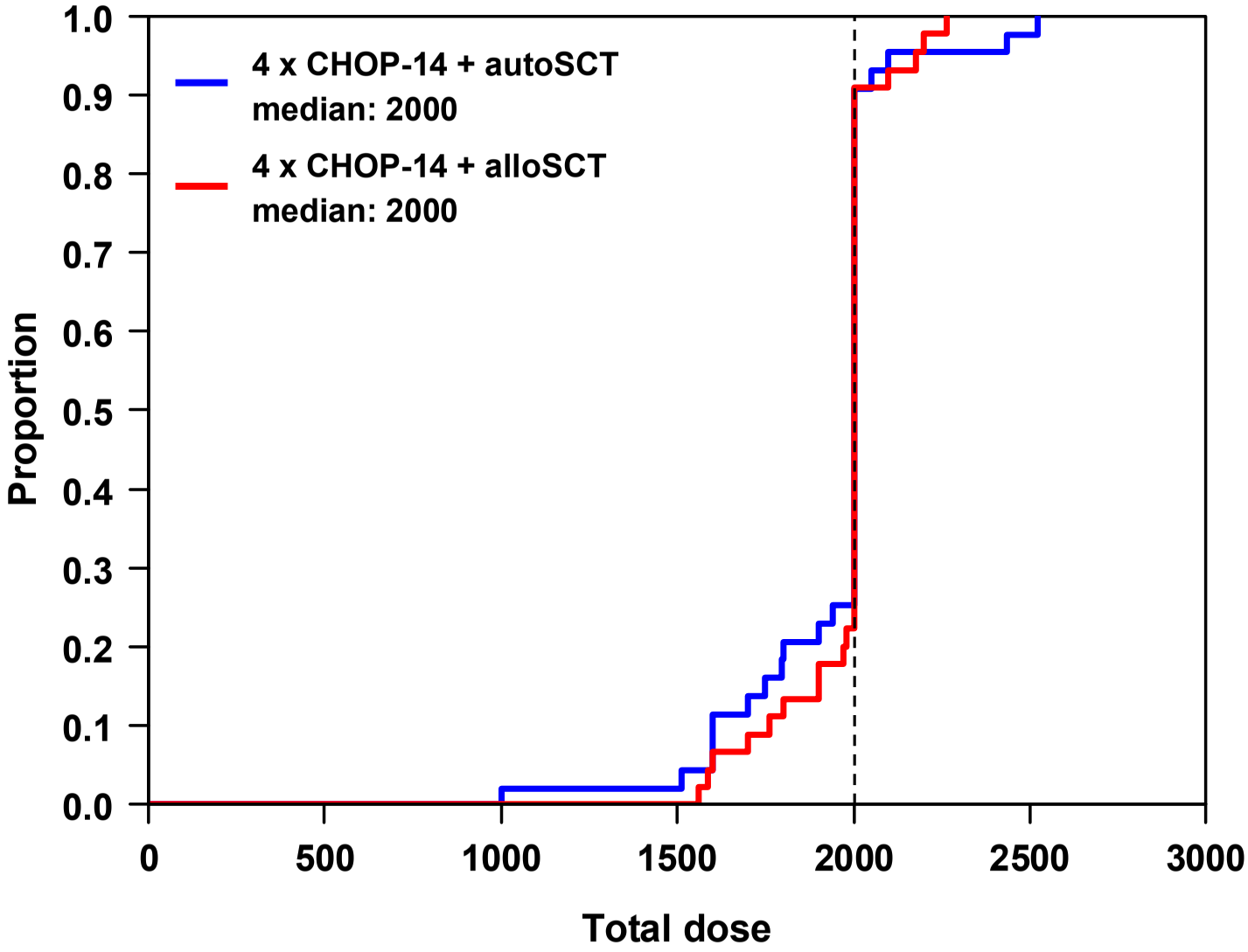
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Absolute dose of Prednisone



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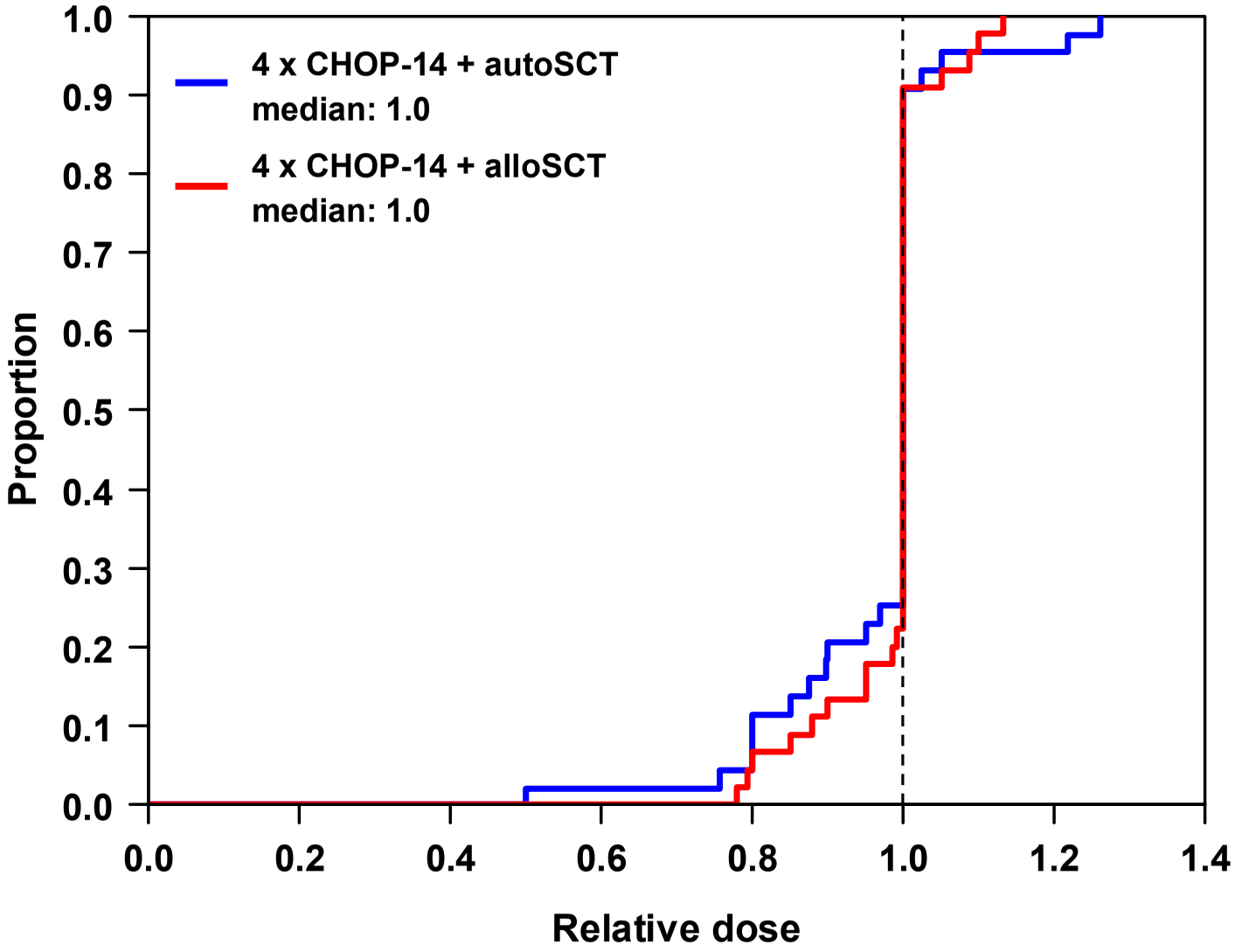
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Relative dose of Prednisone



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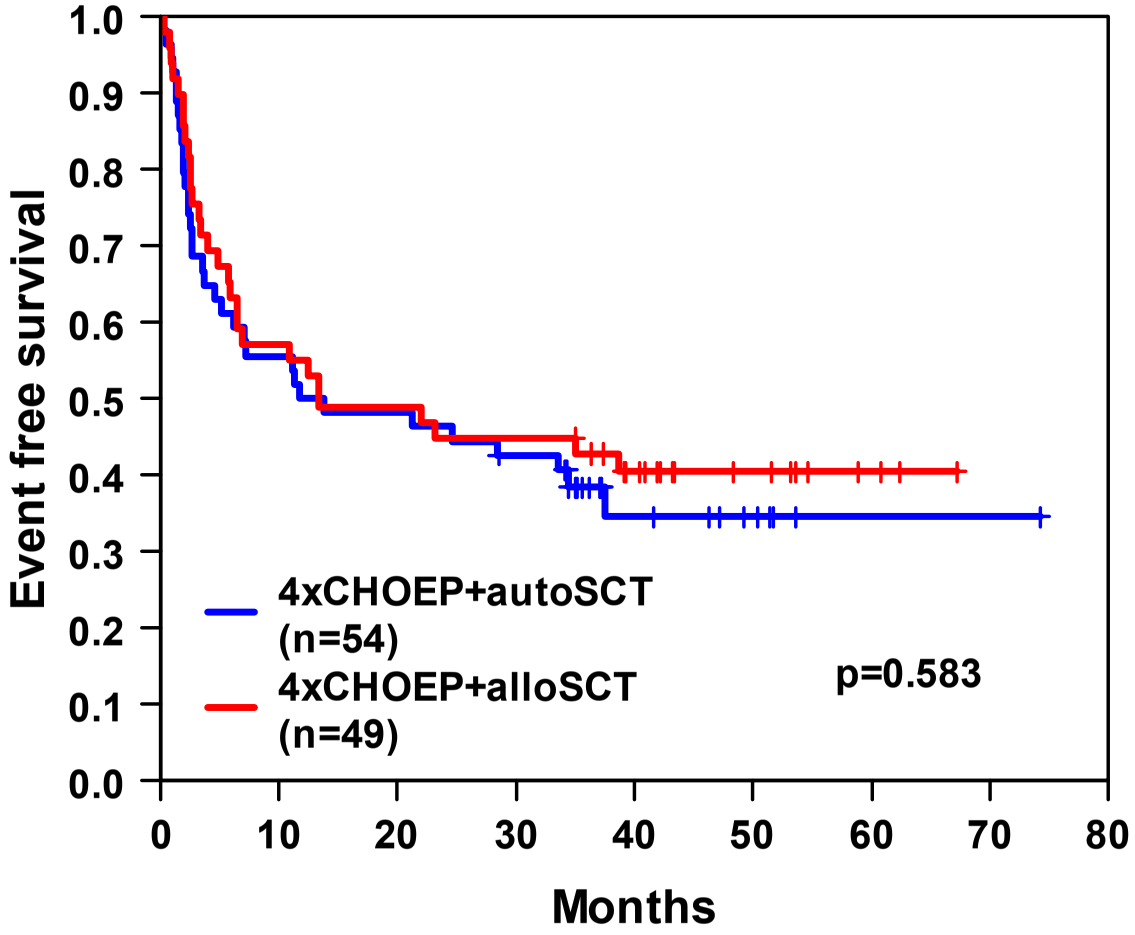
Appendix 3

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

EFS according to treatment arm



Under risk								
4xCHOEP+autoSCT	30	26	22	9	5	1	1	0
4xCHOEP+alloSCT	28	24	22	15	8	3	0	0

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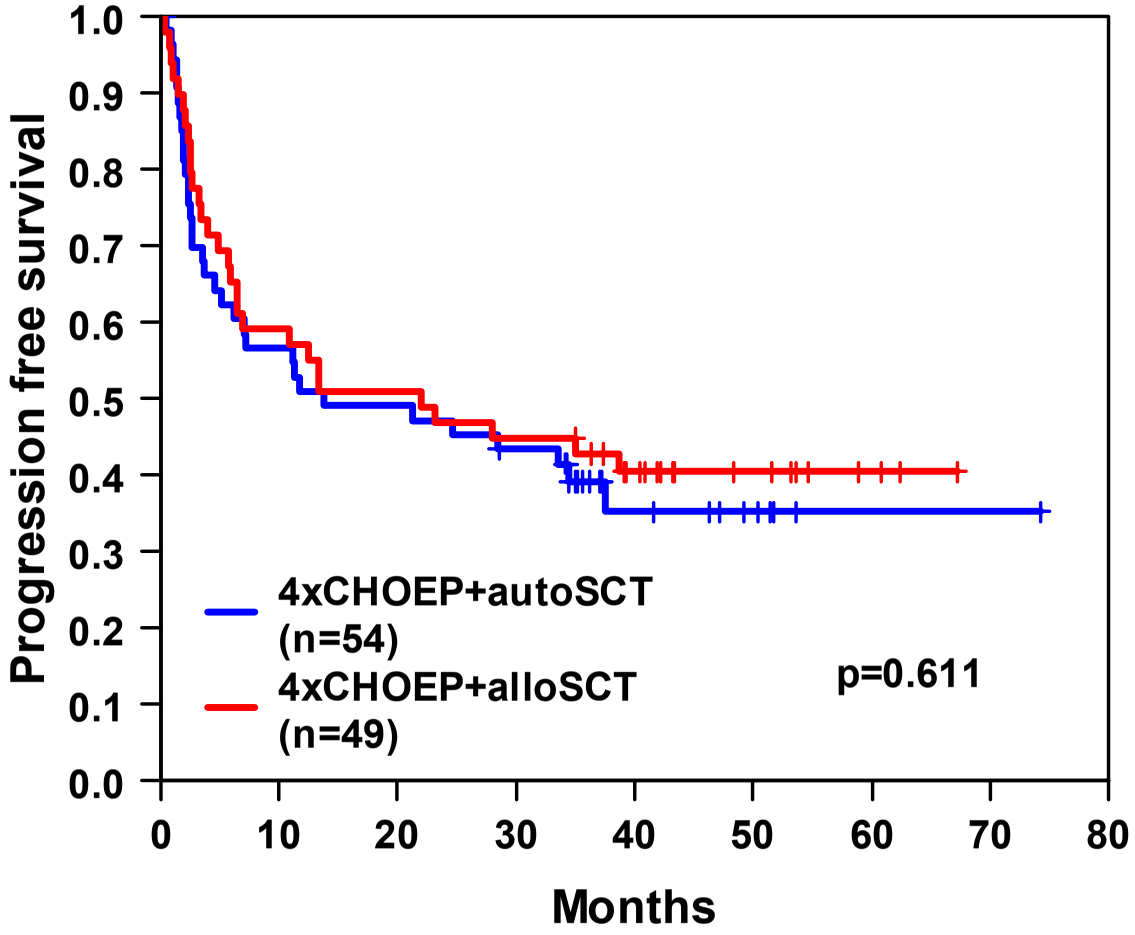
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

PFS according to treatment arm



Under risk								
4xCHOEP+autoSCT	30	26	22	9	5	1	1	0
4xCHOEP+alloSCT	29	25	22	15	8	3	0	0

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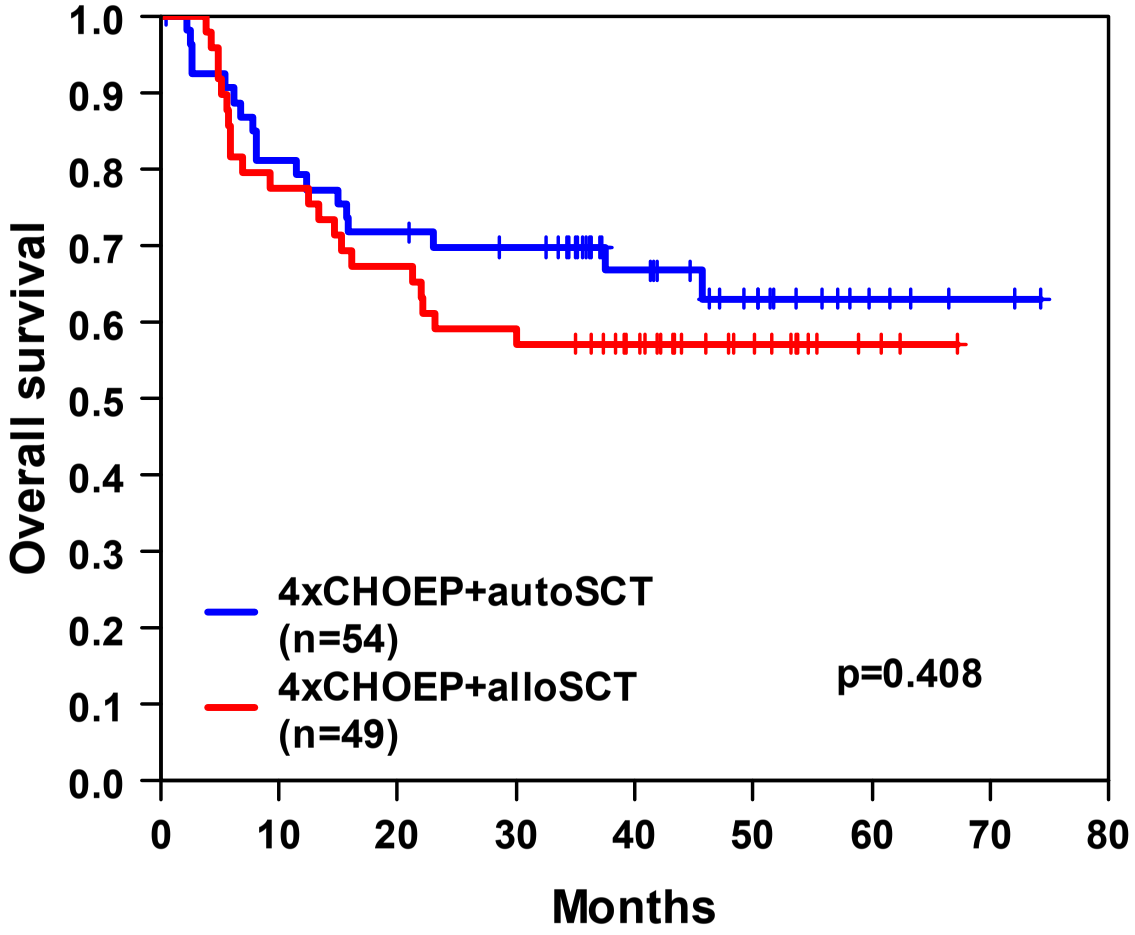
DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

OS according to treatment arm



Under risk								
4xCHOEP+autoSCT	43	38	35	22	14	5	2	0
4xCHOEP+alloSCT	38	33	28	22	12	3	0	0

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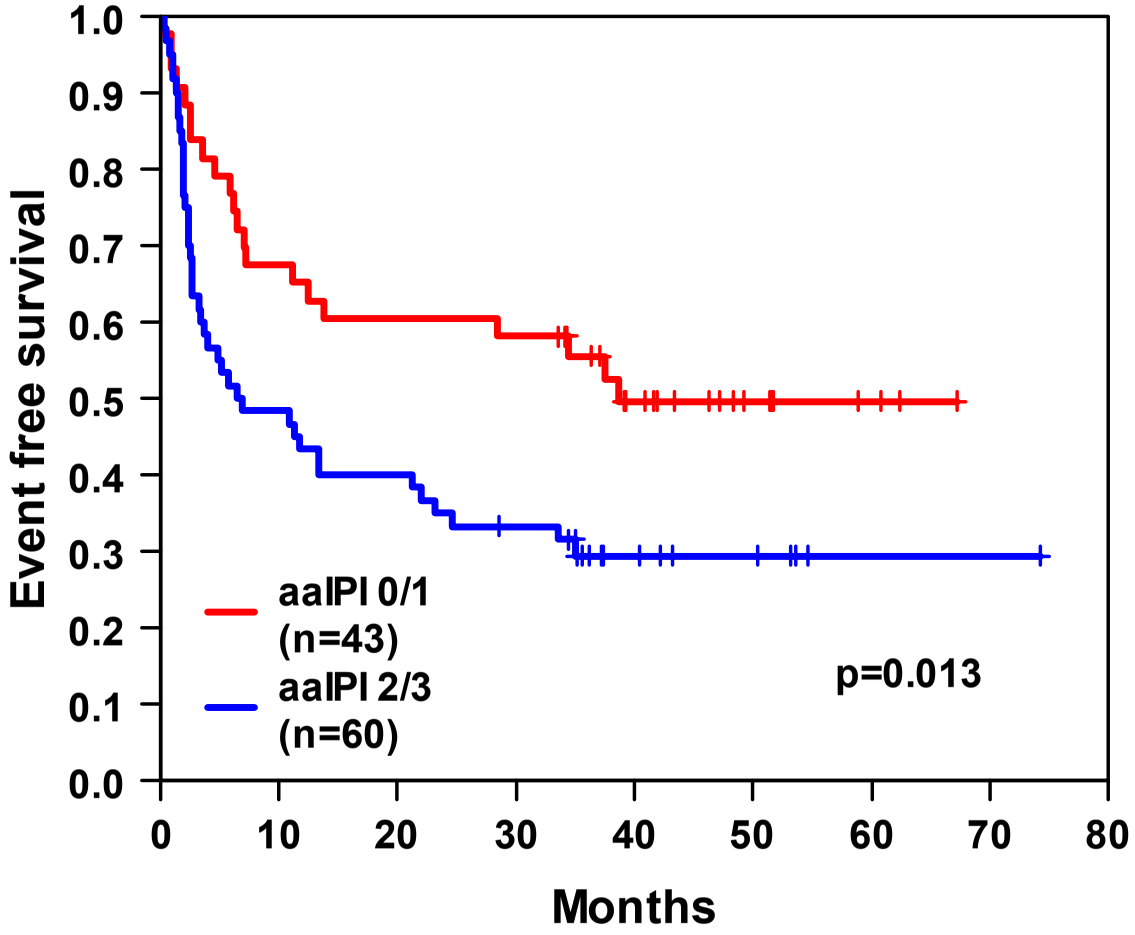
Appendix 4

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

EFS according to aaIPI



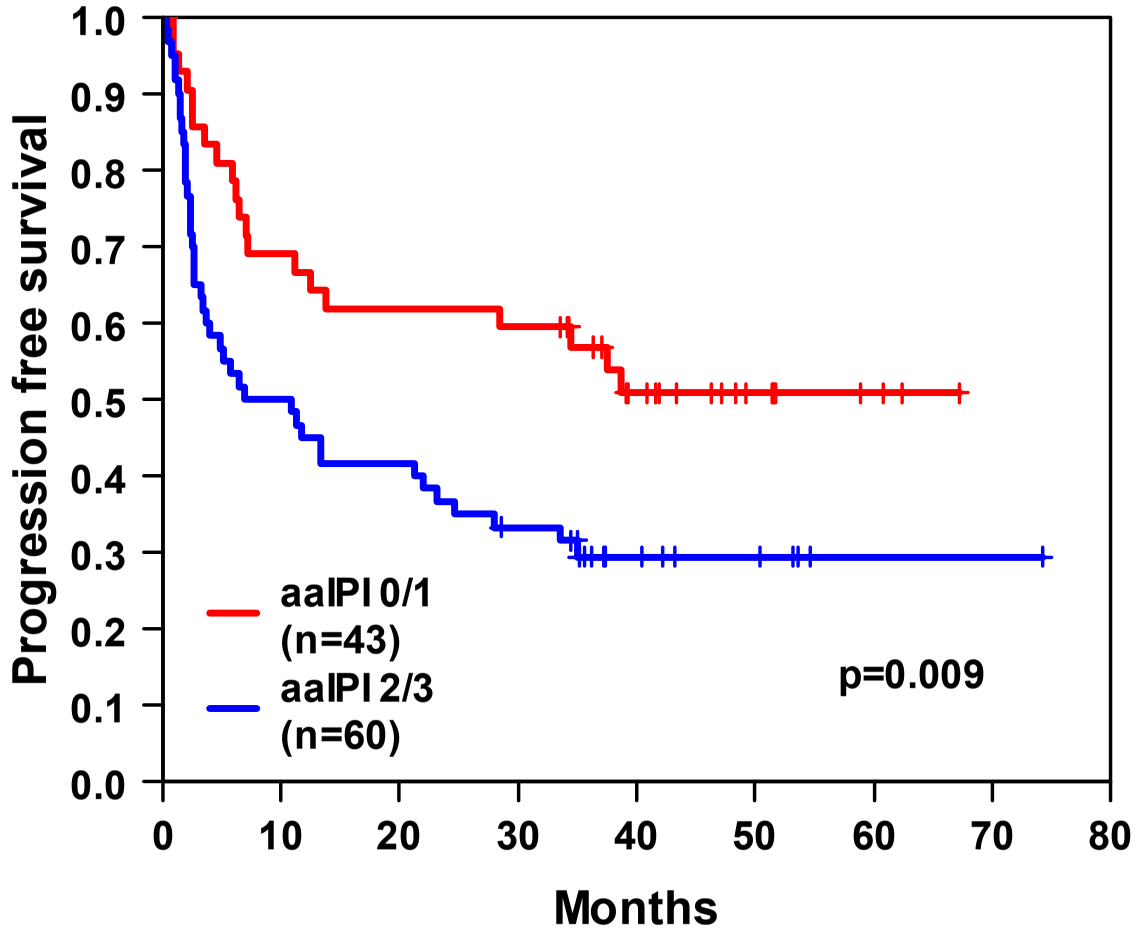
Under risk								
aaIPI 0/1	29	26	25	15	7	3	0	0
aaIPI 2/3	29	24	19	9	6	1	1	0

DSHNHL 27.11.18

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

PFS according to aaIPI



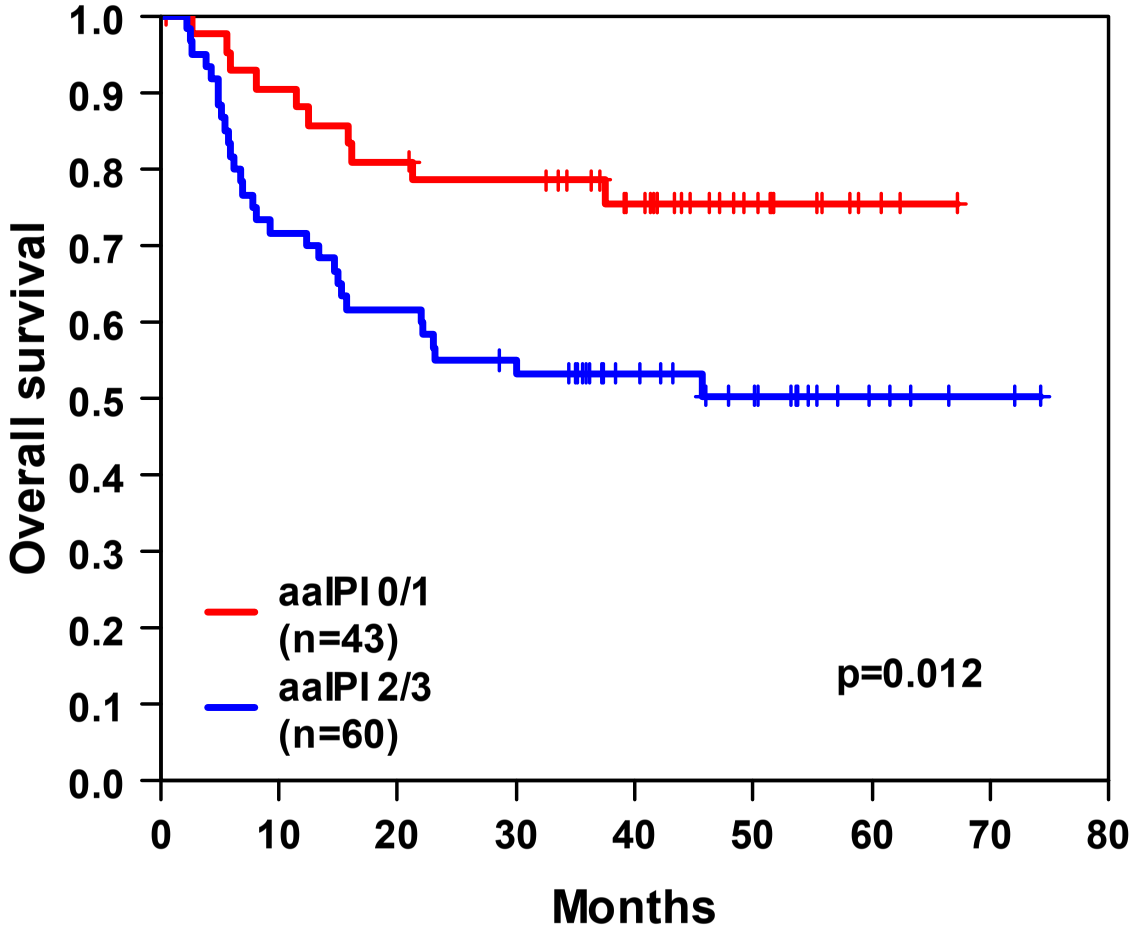
Under risk								
aaIPI 0/1	29	26	25	15	7	3	0	0
aaIPI 2/3	30	25	19	9	6	1	1	0

DSHNHL 27.11.18

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

OS according to aaIPI



Under risk								
aaIPI 0/1	38	34	32	23	11	3	0	0
aaIPI 2/3	43	37	31	21	15	5	2	0

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Appendix 5

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Leukocytopenia during 4xCHOEP-14 over all cycles

CTC	% cycles		
	4xCHOEP-14 + autologous SCT	4xCHOEP-14 + allogeneic SCT	Total
0 (≥ 4 * 10^3/ mm^3)	17	14	16
1 (< 4 * 10^3/ mm^3)	4	3	4
2 (< 3 * 10^3/ mm^3)	14	12	13
3 (< 2 * 10^3/ mm^3)	22	20	21
4 (< 1 * 10^3/ mm^3)	42	51	46

within nadir interval: day 8-10

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Thrombocytopenia during 4xCHOEP-14 over all cycles

CTC	% cycles		
	4xCHOEP-14 + autologous SCT	4xCHOEP-14 + allogeneic SCT	Total
0 (≥ 100 * 10^3/ mm^3)	54	51	53
1 (< 100 * 10^3/ mm^3)	16	13	15
2 (< 75 * 10^3/ mm^3)	15	13	14
3 (< 50 * 10^3/ mm^3)	8	13	10
4 (< 25 * 10^3/ mm^3)	7	11	8

within nadir interval: day 10-12

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Anemia during 4xCHOEP-14 over all cycles

CTC	% cycles		
	4xCHOEP-14 + autologous SCT	4xCHOEP-14 + allogeneic SCT	Total
0 (≥ 11.0 g/ dl)	22	21	22
1 (< 11.0 g/ dl)	19	25	22
2 (< 10.0 g/ dl)	40	41	41
3 (< 8.0 g/ dl)	16	13	14
4 (< 6.5 g/ dl)	3	0	1

Appendix 6

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Adverse events during 4xCHOEP-14 over all cycles I

Event	Number of cycles with CTC grade 3 - 5 / number of documented cycles		
	4xCHOEP-14 + autologous SCT (n=193)	4xCHOEP-14 + allogeneic SCT (n=186)	Total (n=379)
Nausea	0/193 (0%)	2/186 (1%)	2/379 (0.5%)
Vomiting	1/193 (0.5%)	0/186 (0%)	1/379 (0.3%)
Diarrhoea	3/193 (2%)	2/186 (1%)	5/379 (1%)
Constipation	0/193 (0%)	1/186 (0.5%)	1/379 (0.3%)
Mucositis/ stomatitis	5/193 (3%)	3/186 (2%)	8/379 (2%)
Cardiac arrhythmia	1/192 (0.5%)	0/185 (0%)	1/377 (0.3%)
Cardiac general	1/192 (0.5%)	0/185 (0%)	1/377 (0.3%)

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Adverse events during 4xCHOEP-14 over all cycles II

Event	Number of cycles with CTC grade 3 - 5 / number of documented cycles		
	4xCHOEP-14 + autologous SCT (n=193)	4xCHOEP-14 + allogeneic SCT (n=186)	Total (n=379)
Haemorrhage/ bleeding	2/193 (1%)	1/186 (0.5%)	3/379 (1%)
Renal	2/193 (1%)	1/186 (1%)	3/379 (3%)
Neuropathy sensory	2/191 (1%)	0/186 (0%)	2/377 (0.5%)
Mood alteration	0/192 (0%)	0/186 (0%)	0/378 (0%)
Allergic reaction/ hypersensitivity	1/193 (0.5%)	0/186 (0%)	1/379 (0.3%)
Infection	18/193 (9%)	16/184 (9%)	34/377 (9%)

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Adverse events during 4xCHOEP-14 per patient I

Event	% of patients with CTC grade 3 - 5		
	4xCHOEP-14 + autologous SCT (n=54)	4xCHOEP-14 + allogeneic SCT (n=49)	Total (n=103)
Nausea	0/54 (0%)	2/49 (4%)	2/103 (2%)
Vomiting	1/54 (2%)	0/49 (0%)	1/103 (1%)
Diarrhoea	2/54 (4%)	2/49 (4%)	4/103 (4%)
Constipation	0/54 (0%)	1/49 (2%)	1/103 (1%)
Mucositis/ stomatitis	4/54 (7%)	3/49 (6%)	7/103 (7%)
Cardiac arrhythmia	1/54 (2%)	0/49 (0%)	1/103 (1%)
Cardiac general	1/54 (2%)	0/49 (0%)	1/103 (1%)

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Adverse events during 4xCHOEP-14 per patient II

Event	% of patients with CTC grade 3 - 5		
	4xCHOEP-14 + autologous SCT (n=54)	4xCHOEP-14 + allogeneic SCT (n=49)	Total (n=103)
Haemorrhage/ bleeding	2/54 (4%)	1/49 (2%)	3/103 (3%)
Renal	2/54 (4%)	1/49 (2%)	3/103 (3%)
Neuropathy sensory	2/54 (4%)	0/49 (0%)	2/103 (2%)
Mood alteration	0/54 (0%)	0/49 (0%)	0/103 (0%)
Allergic reaction/ hypersensitivity	1/54 (2%)	0/49 (0%)	1/103 (1%)
Infection	10/54 (19%)	12/49 (24%)	22/103 (21%)

Appendix 7

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Types of infections during 4xCHOEP-14 (grade 3-5)

Type of infection	4xCHOEP-14 + autologous SCT (n=18)	4xCHOEP-14 + allogeneic SCT (n=16)	Total (n=34)
Bacterial	10/18 (56%)	9/16 (56%)	19/34 (56%)
Fungal	6*/18 (33%)	2*/16 (12%)	8*/34 (24%)
Viral	2/18 (11%)	2**/16 (12%)	4/34 (12%)
Unknown	12/18 (67%)	11/16 (69%)	23/34 (68%)

***2 (1/1) Aspergillus**
****1 CMV**

Remark: several types of infections can be specified for one infection

Appendix 8

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Haematological toxicity during DHAP

CTC	% patients		
	4xCHOEP-14 + autologous SCT (n=38)	4xCHOEP-14 + allogeneic SCT (n=39)	Total (n=77)
Leukocytopenia CTC= 4	18	38	30
Thrombocytopenia CTC= 3, 4	72	77	75
Anaemia CTC= 3, 4	27	13	20

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Adverse events during DHAP per patient I

Event	% of patients with CTC grade 3 - 5		
	4xCHOEP-14 + autologous SCT (n=38)	4xCHOEP-14 + allogeneic SCT (n=39)	Total (n=77)
Nausea	1/38 (3%)	0/38 (0%)	1/76 (1%)
Vomiting	1/38 (3%)	0/38 (0%)	1/76 (1%)
Diarrhoea	1/38 (3%)	1/38 (3%)	2/76 (3%)
Constipation	0/38 (0%)	0/38 (0%)	0/76 (0%)
Mucositis/ stomatitis	1/38 (3%)	0/38 (0%)	1/76 (1%)
Cardiac arrhythmia	0/38 (0%)	0/38 (0%)	0/76 (0%)
Cardiac general	0/38 (0%)	0/38 (0%)	0/76 (0%)

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Adverse events during DHAP per patient II

Event	% of patients with CTC grade 3 - 5		
	4xCHOEP-14 + autologous SCT (n=38)	4xCHOEP-14 + allogeneic SCT (n=39)	Total (n=77)
Haemorrhage/ bleeding	0/38 (0%)	0/38 (0%)	0/76 (0%)
Renal	0/38 (0%)	1/38 (3%)	1/76 (1%)
Neuropathy sensory	0/38 (0%)	0/38 (0%)	0/76 (0%)
Mood alteration	0/38 (0%)	0/38 (0%)	0/76 (0%)
Allergic reaction/ hypersensitivity	0/38 (0%)	1/38 (3%)	1/76 (1%)
Infection	3*/38 (8%)	0/38 (0%)	3/76 (4%)

***type of infection: 1x bacterial, 2x unknown**

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, FAS (n=103)

Therapeutic interventions during DHAP per patient

	4xCHOEP-14 + autologous SCT (n=38)	4xCHOEP-14 + allogeneic SCT (n=39)	Total (n=77)
Antibiotics interventional	9/38 (24%)	6/39 (15%)	15/77 (19%)
Red blood cell transfusions	12/38 (32%)	10/39 (26%)	22/77 (29%)
Platelet transfusions	14/38 (37%)	8/39 (21%)	22/77 (29%)

Appendix 9

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, PPS4 (n=67)

Adverse events during BEAM/FBC per patient (n=67) I

Event	% of patients with CTC grade 3 - 5		
	BEAM/autologous SCT (n=41)	FBC/allogeneic SCT (n=26)	Total (n=67)
Nausea	2/40 (5%)	2/26 (8%)	4/66 (6%)
Vomiting	1/40 (2%)	1/26 (4%)	2/66 (3%)
Diarrhoea	4/40 (10%)	3/26 (12%)	7/66 (11%)
Constipation	0/41 (0%)	0/26 (0%)	0/67 (0%)
Mucositis/ stomatitis	13/41 (32%)	6/26 (23%)	19/67 (28%)
Cardiac arrhythmia	1/40 (2%)	1/25 (4%)	2/65 (3%)
Cardiac general	1/41 (2%)	0/26 (0%)	1/67 (1%)

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, PPS4 (n=67)

Adverse events during BEAM/FBC per patient (n=67) II

Event	% of patients with CTC grade 3 - 5		
	BEAM/autologous SCT (n=41)	FBC/allogeneic SCT (n=26)	Total (n=67)
Haemorrhage/ bleeding	2/41 (5%)	1/26 (4%)	3/67 (4%)
Renal	0/41 (0%)	4/26 (15%)	4/67 (6%)
Neuropathy sensory	0/41 (0%)	0/26 (0%)	0/67 (0%)
Mood alteration	0/41 (0%)	1/26 (4%)	1/67 (1%)
Allergic reaction/ hypersensitivity	0/40 (0%)	0/26 (0%)	0/66 (0%)
Infection	13/41 (32%)	10/26 (38%)	23/67 (34%)
Hepatotoxicity (other than VOD)	-	1/26 (4%)	-
VOD (venous occlusive disease)	-	0/26 (0%)	-

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DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, PPS4 (n=67)

Adverse events during BEAM/FBC:

Types of infections (grade 3-5)

Type of infection	BEAM/autologous SCT (n=13)	FBC/allogeneic SCT (n=10)	Total (n=23)
Bacterial	10*/13 (77%)	7/10 (70%)	17/23 (74%)
Fungal	1/13 (8%)	0/10 (0%)	1/23 (4%)
Viral	1/13 (8%)	4**/10 (40%)	5/23 (22%)
Other	0/13 (0%)	1***/10 (10%)	1/23 (4%)
Unknown	10/13 (77%)	9/10 (90%)	19/23 (83%)

Remark: several types of infections can be specified for one infection

***1 x Mycobacterium**
****2 x CMV**
***** 1 x Septic shock of unknown origin**

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, PPS4 (n=67)

Therapeutic interventions during BEAM/FBC per patient I

	BEAM/autologous SCT (n=41)	FBC/allogeneic SCT (n=26)	Total (n=67)
Antibiotics interventional	40/41 (98%)	22/26 (85%)	62/67 (93%)
Red blood cell transfusions	40/41 (98%)	25/26 (96%)	65/67 (97%)
Platelet transfusions	34/41 (83%)	25/26 (96%)	59/67 (88%)

Appendix 10

DSHNHL 2006-1A/AATT study (phase III)

Patients 18 - 60 years, T-cell, PPS4 (n=67)

Reason of therapy related death

Therapy related death (study treatment)	4xCHOEP-14 + allogeneic SCT (n=8)	Cause of death
until day 100 after transplantation	4	- acute GvHD - GvHD - CMV pneumonia - unknown infection during aplasia with multiorgan failure
until 1 year after transplantation	2	- hepatic failure due to aggressive post-transplant B-cell-NHL, EBV associated (D-CRF); severe acute GvHD - not resolved (GvHD-CRF) - Varicella-Encephalitis septicaemia
late therapy related death	2	- chronic GvHD - 1 year, 6 months after transplantation - sepsis, pneumonia - 1 year, 7 months after transplantation (D-CRF); chronic GvHD - not resolved (GvHD-CRF)