

Clinical Study Report

Cyclophosphamide as graft-versus-host prophylaxis after allogeneic stem cell transplantation for multiple myeloma. A phase II study

Name of Investigational Product:	Cyclophosphamide		
Indication:	Multiple Myeloma		
Sponsor:	University Medical Center Hamburg Eppendorf Martinistraße 52 20246 Hamburg Germany		
Protocol Number:	Allo-MM-PostCy-Study		
EudraCT Number:	2016-002557-38		
Development Phase:	Phase II		
Study Initiation Date:	First Patient Consented:	10 APR 2018	
	First Patient Dosed:	30 APR 2018	
Study Completion Date:	Last Patient Dosed:	05 DEC 2020	
	Last Follow-up Visit:	01 DEC 2022	
Coordinating Investigator:	Nicolaus Kröger Department of Stem Cell Transplantation University Medical Center Hamburg-Eppendorf Martinistraße 52 20246 Hamburg, Germany		
Version/Date of Report:	Final; 26 MAR 2025		

Sponsor Signature Page

This Synopsis of the Final Clinical Study Report has been approved by:

Coordinating Investigator Signature

I hereby confirm that I have read this Synopsis of the Final Report and confirm that it describes the conduct and the results of the study.



Coordinating Investigator Signature

28 MAR 2025

Date

Prof. Dr. Nicolaus Kröger

Coordinating Investigator Name

Statistician Signature

I hereby confirm that I have read this Synopsis of the Final Report and confirm that it describes the conduct and the results of the study.



Statistician Signature

28 MAR 2025

Date

BEATRICE CHARAMBA

Statistician Name

CLINICAL STUDY REPORT SYNOPSIS

NAME OF SPONSOR/COMPANY: University Medical Center Hamburg Eppendorf	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Cyclophosphamide		
NAME OF ACTIVE INGREDIENT(S): Cyclophosphamide		
Title of Study: Cyclophosphamide as graft-versus-host prophylaxis after allogeneic stem cell transplantation for multiple myeloma. A phase II study.		
Protocol Number: Allo-MM-PostCy-Study EudraCT Number: 2016-002557-38		
Coordinating Investigator: Nicolaus Kröger Department of Stem Cell Transplantation University Medical Center Hamburg-Eppendorf Martinistraße 52 20246 Hamburg, Germany Telephone: +49 (0) 40 7410 54851 Fax: +49 (0) 40 7410 53795 e-mail: n.kroeger@uke.de		
Study Centers: 3 German Study Centers: 1. University Medical Center Hamburg-Eppendorf 2. Heidelberg University Hospital 3. University Medical Center Mainz		
Publication (Reference): not applicable		
Study Period: 10-April-2018 (First Patient In) 01-DEC-2022 (Last Patient Out)		Phase of development: Phase II
Objectives: Primary Objective: The primary objective of the study was to show as primary endpoint chronic GvHD and progression-free survival at 2 years after stem cell transplantation in multiple myeloma in comparison to a historical group.		

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Secondary Objectives: - The present study further evaluated the incidence of acute and chronic GvHD at 2-years, the 2-year risk of non-relapse mortality (NRM), the 2-year progressive-free, and overall survival (OS) in patients who received a toxicity-reduced conditioning regimen combined of thiotepa and busulfan followed by allogeneic stem cell transplantation (SCT) from matched or mismatched, related or unrelated donor, and cyclophosphamide as post-transplant GvHD prophylaxis. - Furthermore, the toxicity and safety of cyclophosphamide as GvHD prophylaxis was determined.		
Methodology: Open label, multicenter phase II trial.		
Number of subjects (planned and analyzed): Planned: 50 patients were planned to be enrolled. Analyzed: 36 patients were analyzed within this study.		
Diagnosis and Main Criteria for Inclusion: ✓ Multiple myeloma newly diagnosed with deletion 17p or translocation 4;14 or multiple myeloma with 1. or 2. relapse after autologous stem cell transplantation (SCT) ✓ Patients age: 18 - 65 years at time of inclusion (female and male) ✓ Performance status Eastern Cooperative Oncology Group (ECOG) ≤ 2 ✓ Availability of haploidentical, matched or mismatched relative or unrelated donor ✓ Patients understand and voluntarily sign an informed consent ✓ Female subjects must either be of non-childbearing potential or use highly effective methods of contraception during the study and 6 months after end of study participation ✓ Male subjects must either have sexual contact who is of non-childbearing potential or use highly effective methods of contraception during the study and 6 months after end of study participation		
Main Criteria for Exclusion: ✓ Severe active infection or other uncontrolled severe conditioning ✓ Severe renal, hepatic, pulmonary or cardiac disease, such as: • Total bilirubin, Serum Glutamic Pyruvic Transaminase (SGPT) or Serum Glutamic Oxaloacetic Transaminase (SGOT) > 3 times upper the normal level • Left ventricular ejection fraction < 30 % • Creatinine clearance < 30 ml/min • Diffusing capacity of lung for carbon monoxide (DLCO) < 35 % and/or receiving supplementary continuous oxygen		

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✓ Positive serology for human immunodeficiency virus (HIV) ✓ Pregnant or lactating women (positive serum pregnancy test) ✓ Women of child-bearing potential with unclear contraception ✓ Age < 18 and > 65 years. ✓ Uncontrolled invasive fungal infection at time of screening (baseline) ✓ Serious psychiatric or psychological disorders ✓ Participation in another study with ongoing use of unlicensed investigational product from 28 days before study enrollment		
Test Product, Dose, Mode of Administration, and Batch No.: <u>Test product:</u> Cyclophosphamide <u>Dose:</u> 2 x 50 mg/kg body weight (BW) <u>Mode of administration:</u> intravenously (iv) <u>Batch numbers:</u> not applicable, since Cyclophosphamide was applied as part of routine treatment		
Duration of Treatment: Patients received on day 3 and 4 after allogeneic stem cell transplantation 50 mg/kg BW cyclophosphamide		
Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable		
Criteria for evaluation: Efficacy: Primary Endpoint: • Chronic GvHD and progression-free survival at 2 years after allogeneic SCT Secondary Endpoints: • Non-Relapse-Mortality (NRM) at 2 years after allogeneic SCT • Incidence of acute GvHD on Day +100 after allogeneic SCT • Incidence of chronic GvHD at 1 and 2 years after allogeneic SCT • Toxicity according to National Cancer Institute (NCI) • Complete remission rate (including stringent complete response [sCR] and minimal residual disease [MRD] negativity) • Overall and progression-free survival at 2 years		

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Statistical methods: Sample size: The chronic (c)GvHD and PFS at 2 years after conventional GvHD prophylaxis is about 15%. An improvement to 35% cGvHD/PFS at 2 years was considered to be a reasonable goal. A sample size of 42 patients provided 90% power to observe a difference at 1-sided 5% type 1 error. To calculate a certain loss 50 patients were to be included. Due to very poor recruitment rates sample size of 42 patients was not reached. Efficacy analysis: Efficacy analyses was done using the FAP population. All statistical tests, including the statistical test of the primary efficacy endpoint, will be two-sided at a significance level of 5%. All reported confidence intervals will be two-sided with confidence level 95%. To compare cGRFS at 2 years after allogeneic SCT between the single arm 'MultMyelom' of this study and historical reference data, a two-sided z-test with a 5.0% significance level was performed and the corresponding two-sided p-value was presented. All secondary efficacy endpoints will be analysed descriptively. Interim Analysis: An interim analysis was planned after 10 patients completing +100 days after allo SCT but was not done. The safety data of the clinical trial were reviewed in regular study meetings. Due to the small number of patients and the open, single-arm study design, it was possible to check throughout the study whether there were any safety concerns without conducting an interim analysis.		
Results Subject Disposition and Demographics: Thirty-six patients were enrolled in this trial, forming the full analysis population as well as the safety population. More males (n=22) than females (n=14) participated and the mean age overall was 53.2 years, range 35 – 66 years. Twenty-six patients (72.2%) relapsed after their 1st autoSCT and 6 patients (16.7%) relapsed after their 2nd SCT. Most patients (n=30, 83.3%) were in the conditioning age group ≤60 years: Thiotepa (2 x 5 mg/kg BW i.v), Busulfan (3 x 3.2 mg/kg BW i.v). In most patients the ECOG performance status at baseline was 0 (fully active, 50%) or 1 (restricted in physically strenuous activity, 47.2%). Regarding comorbidities pulmonary disease and obesity were the ones mostly present in the patient population.		

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Efficacy variables:

Primary endpoint:

The primary endpoint was chronic GvHD and progression-free survival at 2 years after allogeneic SCT. The survival probability at 2 years was 38.9% (25.8% - 58.6%). In comparison with the historical group, this probability was significantly different (p-value =0.003).

Comparison of cGRFS at 2 years after SCT between patients with multiple myeloma and historical reference data – FAP

Time from SCT	Survival Function estimate	Standard error	95% lower CI	95% upper CI	Z value	P value
2 years	0.389	0.081	0.258	0.586	2.940	0.003

Secondary endpoints:

The cumulative incidence rate of non-relapse mortality starting from SCT was 11.1% (CI 3.5% - 23.8%) after 1 year as well as after 2 years. The probability of experiencing a relapse was 13.9% (5.0% - 27.3%) after 1 year and increased to 47.2% (30.1% - 62.6%) after 2 years.

An acute GvHD with toxicity grade II-IV at Day 100 was noted in 4 patients (11.1%). Out of those there were 2 patients (5.6%) with a GvHD grade III-IV.

The cumulative incidence of chronic GvHD was 41.7% (25.3% - 57.3%) after 1 year as well as after 2 years.

The cumulative incidence of death before chronic GvHD was estimated to be 19.4% (8.4% - 33.9%) at 1 year and it was estimated to be 22.2% (10.2% - 37.1%) at 2 years.

The probability of experiencing complete remission rate including sCR (from SCT) was 63.9% (45.4% - 77.5%) after 1 year and 77.8% (59.3% - 88.6%) after 2 years. The median remission duration was 1194.5 days (range 229 days – 2769 days).

Progression free survival from SCT was 75% (62.1% - 90.6%) after 1 year and 41.7% (28.3% - 61.3%) after 2 years. The median survival time for PFS from SCT was 19.1 months.

Overall survival from SCT was 80.6% (68.6% - 94.6%) at 1 year and 72.2% (59.0% - 88.4%) after 2 years. Median overall survival was not reached at the end of study period.

Safety and tolerability:

All patients had at least 1 AE in this study both before and after intake of the investigational medicinal product. Overall, most AEs were reported in the SOC infections and infestations (n=21, 63.6%) and in the SOC general disorders and administration site conditions (n=20, 60.6%). In this SOC the preferred

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terms that were reported with high frequency were mucosal inflammation (n=16, 48.5%) and pyrexia (n=12, 36.4%). Severe AEs regarding transplantation after cyclophosphamide were also mostly recorded in the SOC General disorders and administration site conditions (n=26) and Infections and infestations (n=37). Considering AEs related to the study treatment, the most frequently observed severe AE was mucosal inflammation that occurred in a total of 6 patients (grade 3 and 4). No new or unexpected severe AE was observed during the study. There were no relevant changes in laboratory investigations, physical findings and vital signs. Therefore, the safety profile of cyclophosphamide seems to be acceptable in this study.		
CONCLUSIONS Allogeneic stem cell transplantation with thiotepa/Busulfan conditioning regimen with PTC as GvHD prophylaxis in multiple myeloma patients who relapsed after autograft showed high survival rate compared to the historical group at 2 years after SCT.		
Date of the report: 26. March 2025		