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Autologous-allogeneic tandem stem cell transplantation and maintenance therapy with thalidomide / DLI for patients with multiple myeloma (MM) and age ≤60 years: A phase II-study

Project ID:	Auto-Allo TSCT in MM
EudraCT No.:	2007-004928-21

Integrated Study Report – Synopsis

Version / date:	1.0 of 07 April 2020
Sponsor, signatory:	Department of Stem Cell Transplantation, University Medical Center Eppendorf, att. Prof. Dr. Nicolaus Kröger, Martinistraße 52, 20246 Hamburg, Germany, phone +49 (0)40 7410 55864, fax +49 (0)40 7410 53795, e-mail nkroeger@uke.de
Design:	Open-label, parallel-group clinical trial, autologous-allogenic versus autologous-autologous tandem stem cell transplantation
First patient in:	14 October 2008
Last patient out:	17 April 2018
Coordinating investigator:	Prof. Dr. Nicolaus Kröger, Department of Stem Cell Transplantation, University Medical Center Eppendorf, Hamburg, Germany

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Signatures

Sponsor's signatory:

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8 APR. 2020

2 Synopsis

Sponsor:	Department of Stem Cell Transplantation, University Medical Center Eppendorf att. Prof. Dr. Nicolaus Kröger, Martinistraße 52, 20246 Hamburg, Germany
Name of finished product:	Thalidomide Celgene 50 mg hard capsules
Active ingredient:	Thalidomide
Title of study:	Autologous-allogeneic tandem stem cell transplantation and maintenance therapy with thalidomide / DLI for patients with multiple myeloma (MM) and age ≤60 years: A phase II-study
Project ID:	Auto-Allo TSCT in MM
EudraCT No.:	2007-004928-21
Investigators and study centers:	23 centers in Germany participated, out of which 20 enrolled any patients:

Center No.	Site	Investigator
001	Universitätsklinikum Hamburg-Eppendorf; Interdisziplinäre Klinik und Poliklinik für Stammzelltransplantation; Hamburg	Prof. Dr. med. Nicolaus Kröger
002	Klinikum der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg; Klinik für Onkologie und Hämatologie; Halle (Saale)	Dr. med. Hans-Heinrich Wolf
003	Asklepios Klinik Hamburg-Altona; II. Medizinische Abteilung; Hamburg	Dr. med. Hans-Jürgen Salwender
004	Medizinische Hochschule Hannover; Klinik für Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation; Hannover	Prof. Dr. med. Dietrich Peest
005	Universitätsklinikum Heidelberg; Medizinische Klinik V; Heidelberg	Prof. Dr. med. Ute Hegenbart

006	HSK, Dr. Horst Schmidt Klinik; Klinik Innere Medizin III; Wiesbaden	Prof. Dr. med. N. Frickhofen
007	Universitätsklinikum Essen; Klinik für Knochenmarktransplantation; Essen	Prof. Dr. med. Dietrich Beelen
008	Klinikum Augsburg; II. Medizinische Klinik / Onkologie/Hämatologie; Augsburg	Prof. Dr. med. Christoph Schmid
009	Robert-Bosch-Krankenhaus; Abteilung für Innere Medizin 2; Stuttgart	Prof. Dr. med. W.-E. Aulitzky
010	Deutsche Klinik für Diagnostik GmbH; Zentrum für Blutstammzell- und Knochenmarktransplantation; Wiesbaden	Prof. Dr. Gernot Stuhler, Dr. med. Rainer Schwerdtfeger
011	Universitätsklinikum Düsseldorf; Klinik für Hämatologie, Onkologie u. Klinische Immunologie; Düsseldorf	Prof. Dr. med. Guido Kobbe
012	Universitätsklinikum Münster; Medizinische Klinik und Poliklinik A; Münster	Prof. Dr. Matthias Stelljes, PD Dr. med. Martin Kropff
013	Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden; Medizinische Klinik und Poliklinik I; Dresden	Prof. Dr. med. Martin Bornhäuser
014*	Ernst-Moritz-Arndt-Universität Greifswald; Medizinische Universitätsklinik C, Hämatologie und Onkologie, Transplantationszentrum; Greifswald	Prof. Dr. C. A. Schmidt, Prof. Dr. med. G. Dölken
015	Klinikum Frankfurt (Oder) GmbH; Medizinische Klinik I, Frankfurt (Oder)	Prof. Dr. med. Michael Kiehl
016	Universitätsmedizin Göttingen; Abteilung Hämatologie/Onkologie; Göttingen	Prof. Dr. med. Gerald Wulf
017	Universitätsklinikum Tübingen; Medizinische Universitätsklinik II; Tübingen	Prof. Dr. med. W. Bethge

018	Universitätsklinikum Gießen und Marburg GmbH; Standort Marburg, Marburg	Prof. Dr. med. Andreas Neubauer
019*	Charité Campus Benjamin Franklin; Medizinische Klinik III; Berlin	Prof. Dr. med. Lutz Uharek
020*	Klinikum der Ludwigs-Maximilians-Universität München; Campus Großhadern; München	Prof. Dr. med. Helmut Ostermann
021	Universitätsklinikum Bonn; Medizinische Klinik und Poliklinik III; Bonn	Prof. Dr. med. Dominik Wolf
022	Universitätsklinikum Magdeburg A.ö.R.; Zentrum für Innere Medizin; Klinik für Hämatologie; Magdeburg	Dr. med. Thomas Heinicke
023	Universitätsmedizin der Johannes Gutenberg-Universität Mainz; III. Med. Hämatologie/Onkologie; Mainz	PD Dr. med. Ralf-Georg Meyer

* Center did not enroll any subjects

Publication (reference): None.

First patient in: 14 October 2008

Last patient out: 17 April 2018

Phase of development: II

Objectives: To investigate whether autologous-allogeneic (Auto-Allo) tandem stem cell transplantation (TSCT), compared to autologous-autologous (Auto-Auto) TSCT, has a beneficial effect on progression-free survival and on other clinically relevant outcomes in patients ≤60 years of age suffering from multiply myeloma (MM).

Methodology: Open-label, parallel-group, multi-center clinical trial in patients ≤60 years of age suffering from MM. Patients received autologous peripheral blood stem cell transplantation (PBSCT) followed by allogeneic PBSCT when a matching stem cell donor could be acquired; otherwise, or if they declined allogeneic PBSCT, they received two autologous PBSCTs. Afterwards patients entered a follow-up period with visits scheduled at 4, 6, 12, 18, 24, 36, and 48 months after the second stem cell transplantation (SCT). Patients in both treatment arms were scheduled to receive thalidomide as maintenance treatment after the second SCT.

Number of patients:

	Second SCT		
	Allogeneic	Autologous	Total
Planned to be treated	~111	~74	185
Included			217
Underwent second SCT	132	46	178
Completed as scheduled	75	19	94
Safety analysis set (SAS)	132	46	178
Full analysis set (FAS)	132	46	178
Per-protocol analysis set (PPS)	79	34	113

Diagnosis and main criteria for inclusion:

Male and female patients, 18 – 60 years of age, suffering from MM Stage II or III according to Salmon and Durie, with a maximum of eight chemotherapy cycles prior to inclusion, and willing and able to comply with the "Thalidomide Pregnancy Prevention Plan for Subjects in Clinical Trials".

Test product, dose and mode of administration, batch number:

The investigational intervention was Auto-Allo TSCT using peripheral blood stem cells harvested from the patient and from a matched donor, respectively.

As a part of their maintenance treatment after TSCT, patients were scheduled to receive thalidomide 100 mg/day (two hard capsules for oral administration containing 50 mg of thalidomide) starting on Day 120 after the second SCT. Thalidomide was manufactured for the study as an investigational medicinal product (IMP).

The following thalidomide batch numbers applied:

Lot. 0297C/P1 (AUG-2010)
Lot. 10 F0447 (FEB-2013)
Lot. 11 F0040 (JUN-2013)
Lot. 12 F0867 (JUL-2014)
Lot. 13 F0457 (DEC-2015)
Lot. 15 F1781 (NOV-2018)

Duration of treatment:

TSCT: one autologous and one allogeneic PBSCT

Thalidomide: administration was to be started at Day 120 after the second SCT and to be continued for a maximum period of two years or until progression or non-tolerable toxicity.

Reference therapy, dose and mode of administration, batch number:

The reference intervention was Auto-Auto TSCT (i. e., two autologous PBSCTs) using peripheral blood stem cells harvested from the patient.

As a part of their maintenance treatment after the second SCT, patients were scheduled to receive thalidomide 100 mg/day (for details, see 'Test product' above).

Criteria for evaluation:	Efficacy:	Primary efficacy outcome measure: relapse/progression-free survival at four years after TSCT Main secondary outcome measures: • cumulative incidence of acute and chronic GvHD (aGvHD, cGvHD) and MM relapse/progression • disease-related mortality • treatment-related (non-relapse) mortality • over-all mortality
	Safety:	• adverse events (AEs) • toxicity of conditioning and maintenance treatment • survival-related endpoints already listed under Efficacy
Statistical methods:	To demonstrate superiority of Auto-Allo TSCT over allo-allo TSCT regarding relapse/progression-free survival, the incidence of failure events (relapse/progression or any cause death) was compared between the treatment groups using Kaplan-Meier survival analysis. Confirmatory testing was performed in the Full Analysis Set (FAS) using a Log Rank test and a two-sided type I error level of α=0.05. All other outcomes were analyzed descriptively. All indicated p-values are two-sided; all confidence intervals (CIs) have a coverage of 95%. The sample size was calculated on the basis of expected 48-month event rates of 50% for Auto-Allo TSCT and of 70% for Auto-Auto TSCT. A total sample size of 185 patients was estimated to provide at least 80% power to reject the null hypothesis in a log-rank test model. An adaptive interim analysis was planned in the study protocol but was actually not performed.	

Summary of results and conclusions:

Efficacy:

In the FAS, cumulative relapse/progression-free survival at 48 months after the second SCT was 0.469 (Greenwood CI: 0.382; 0.551) for Auto-Allo TSCT and 0.350 (0.214; 0.489) for Auto-Auto TSCT, with median survival times of 40.1 and of 29.8 months (Log-rank test: p=0.260) and crude failure event rates of 53.0% and 63.0%, respectively. Sixty-two out of 132 patients (47.0%) in the Auto-Allo group survived progression-free compared to 17 out of 46 (37.0%) in the Auto-Auto group.

During the initial 48 months after the second SCT 53 (40.2%) patients in the Auto-Allo group and 28 (60.9%) in the Auto-Auto group showed progression or relapse of MM. The corresponding cumulative incidences (using death in remission as a competing risk) were 0.402 (CI: 0.327; 0.496) and 0.629 (0.501; 0.789) for Auto-Allo and Auto-Auto TSCT, respectively (Gray's test: 0.011).

Disease-related mortality was assessed by means of cumulative incidence analysis using death without prior relapse/progression as a competing risk. In the Auto-Allo group 28 patients (21.2%) died following relapse or progression, compared to 14 (30.4%) in the Auto-Auto group. Forty-eight-month cumulative incidence of disease-related mortality was 0.213 (CI: 0.153; 0.296) and 0.322 (0.209; 0.496) for Auto-Allo and Auto-Auto TSCT, respectively (Gray's test: 0.154).

In the Auto-Allo group 17 patients (12.9%) died without prior relapse or progression within four years of the second SCT, compared to one patient (2.2%) in the Auto-Auto group. The cumulative 48-month incidence of treatment-related (non-relapse) mortality (using relapse / progression as a competing risk) was 0.129 (CI: 0.083; 0.201) and 0.022 (0.003; 0.151) for Auto-Allo and Auto-Auto TSCT, respectively (Gray's test: 0.044).

Forty-five out of 132 patients in the Auto-Allo group (34.1%) and 15 patients out of 46 in the Auto-Auto group 32.6% died for any reason within 48 months after the second SCT. Cumulative 48-month survival was 0.658 (CI: 0.571; 0.733) for Auto-Allo TSCT and 0.657 (0.495; 0.777) for Auto-Auto TSCT (Log-rank test: p=0.906; Kaplan-Meier survival analysis).

Acute graft versus host disease (GvHD) after allogeneic SCT or after donor lymphocyte infusion (DLI) was observed at least once in 72 patients undergoing Auto-Allo TSCT, with a 48-month cumulative incidence of 0.550 (CI: 0.471; 0.642). Eighty-one patients in the Auto-Allo group suffered from at least one episode of chronic GvHD (48-month cumulative incidence with CI: 0.614 [0.536; 0.703]).

Safety: Between study inclusion and the end of the period of observation, a total of 1,874 adverse events (AEs) were reported in 130 patients (98.5% of 132) in the Auto-Allo group, compared to 630 events in 46 patients (100%) in the Auto-Auto group. Incidences of AEs of any kind were 0.0109 and 0.0105 events per patient day, or 13.95 and 13.22 events per patient, for Auto-Allo and Auto-Auto, respectively. Incidences of AEs with CTC grade 3 or higher or with intensity = 'severe' were 0.0010 (or 1.31 events per patient) for Auto-Allo and 0.0007 (or 0.87 events per patient) for Auto-Auto TSCT.

One hundred and fifty-one AEs (8.1% of 1,874) reported by 61 patients (46.2% of 132) in the Auto-Allo group and 87 of 630 AEs (13.8%) reported by 31 patients (67.4% of 46) in the Auto-Auto group were assessed to be potentially related to thalidomide (causal relationship definite, probable, or unknown / not assessed) during open-label evaluation. The most frequently reported, potentially related events were polyneuropathy (32 patients), constipation (18 patients), fatigue (12 patients), peripheral sensory neuropathy (11 patients), and muscle spasms (10 patients).

A total of 281 serious AEs were reported in 103 patients (78.0%) in the Auto-Allo group, compared to 62 serious events in 32 patients (69.6%) in the Auto-Auto group. The most frequent serious events were polyneuropathy (Auto-Allo 17.4% of patients; Auto-Auto 19.6%), constipation (6.1% and 21.7%), fatigue (6.8% and 6.5%, and peripheral sensory neuropathy (4.5% and 10.9%).

Forty-five out of 132 patients in the Auto-Allo group (34.1%) and 15 patients out of 46 in the Auto-Auto group 32.6% died for any reason within 48 months after the second SCT. The leading single cause of death was recurrence or progression of MM (Auto-Allo 12 patients, 9.1%; Auto-Auto 8, 17.4%). In the Auto-Allo group 17 patients 12.9%) died from an infection or from GvHD and 8 (6.1%) died from organ failure not associated with GVHD or infection whereas death due to these causes was not observed in the Auto-Auto group.

Conclusions: In this phase II study Auto-Allo TSCT, as compared to Allo-Allo TSCT, reduced the rate of MM recurrence or progression by about 1/3, from 61% to 40%, during a four-year follow-up. During the same period, Auto-Allo TSCT was also associated with a reduction of disease-related mortality by about 1/3, from 30% to 21%. However, since the non-relapse mortality rate in patients receiving Auto-Allo TSCT was substantially higher than in patients receiving Auto-Auto TSCT, a statistically non-significant advantage of about 10% favoring Auto-Allo TSCT was observed for the primary outcome measure, relapse/progression-free survival. In the Auto-Allo group, leading cases of non-relapse mortality were infections, organ failure, and acute or chronic GvHD. Evident advantages of Auto-Allo TSCT over Auto-Auto TSCT in regarding the prevention of MM relapse or progression, including disease-related mortality, were thus partly reversed by a higher risk of non-relapse mortality.

While the over-all rate of AEs was comparable in both treatment groups, patients who received Auto-Allo TSCT tended to have slightly more severe and also more serious AEs that those in the Auto-Auto group.

Across both groups, about 10% of all AEs were assessed to be causally related to the administration of thalidomide administered as prophylactic treatment after TSCT.

Date of synopsis: 07 April 2020