# Studientitel:

**A PHASE II STUDY TO INVESTIGATE THE EFFICACY OF CYCLOPHOSPHAMIDE AS SOLE GRAFT-VERSUS-HOST-PROPHYLAXIS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (OCTET-CY)**

**Prüfsubstanz:** Cyclophosphamid nach allogener Stammzelltransplantation

**Eudra-CT Nummer:** 2010-022058-18

**Kurzbezeichnung:** OCTET-CY

# Abschlussbericht (Zusammenfassung)

**(Draft) 2.0 / Datum: 15.01.2015**

## Sponsor der klinischen Prüfung:

Cologne University

Albertus-Magnus-Platz

50923 Köln

Germany

## Leiter der klinischen Prüfung / Hauptprüfer:

Prof. Dr. med. Christof Scheid

## Autor des Abschlussberichtes:

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**Studienbeginn – Studienabschluss**

14.03.2011 – 10.08.2013

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|---|---|
| **Titel der Studie** | **A PHASE II STUDY TO INVESTIGATE THE EFFICACY OF CYCLOPHOSPHAMIDE AS SOLE GRAFT-VERSUS-HOST-PROPHYLAXIS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (OCTET-CY)** |
| **Amendments** | No amendments |
| **Art des Vorhabens** | AMG, Phase II |
| **Sponsor / Vertreter** | Cologne University<br>Albertus-Magnus-Platz<br>50923 Cologne<br>Germany<br>Represented by:<br>PD Dr. C. Scheid (Principal investigator)<br>Dept. I of Internal Medicine<br>Cologne University Hospital<br>Kerpener Strasse 62<br>50937 Cologne<br>Germany |
| **Leiter der klinischen Prüfung** | See above |
| **Hauptprüfer in verschiedenen Zentren** | n.a. |
| **Studienzentren:** | Cologne |
| **Veröffentlichung der Studie (Reference)** | Manuscript submitted to European Journal of Hematology |
| **Studienzeitraum** | 14.03.2011 – 10.08.2013 |
| **Studienziele** | To assess the efficacy of post-transplantation cyclophosphamide as single-agent GvHD prophylaxis after allogeneic hematopoietic stem cell transplantation in patients with multiple myeloma or lymphoma and to describe the influence of the modified immunosuppression concept on relapse rates, minimal residual disease, immune reconstitution and chimerism. |
| **Primärer Zielparameter** | Number of patients not requiring any additional immunosuppressive treatment until day 100 after allogeneic transplantation. - As the main aim of this pilot study is to test post-transplant Cy as single-agent immunosuppression, the ab- |

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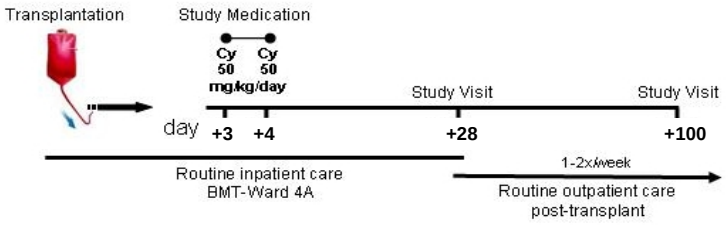
| | sence of systemic immunosuppression at d+100 has been defined as primary endpoint. It is measured as the proportion of patients not requring additional immunosuppressive treatment for GVHD until day 100. |
| **Sekundäre Zielparameter** | – Cumulative incidence and severity of acute GvHD<br>– Cumulative incidence of relapse<br>– Non-relapse-mortality at day +28 and +100<br>– Overall survival at day +100<br>– Haematopoietic reconstitution<br>– Donor chimerism<br>– Immune reconstitution |
| **Studiendesign** | – Single centre, single arm prospective phase II clinical trial with two-stage Simon's adaptive design<br>– Patient numbers: 5 for interim analysis, 11 total evaluable, 13 maximum.<br>– Interim Analysis after 5 patients<br>– Single-arm, unblinded<br>– Consent/ inclusion d+2 after allo-transplant; study medication given on d+3 and +4 after allo-transplant; study visits on day+28 and day+100 after allo-transplant; routine follow-up in bmt outpatient department (see schedule)<br>– The observation time lasts from day +3 to day +100.<br>  |
| **Prüfmedikation / Behandlungsstrategie** | Cyclophosphamide 50mg/ kg body weight/ day given on day +3 and +4 after allogeneic stem cell transplantation as single-agent graft-versus-host disease prophylaxis |
| **Behandlung/Intervention** | Cyclophosphamide 50mg/ kg body weight/ day given intravenously on day +3 and +4 over 1 hour; concomittant medication: Dose-adapted Mesna for the prevention of hemorrhagic cystitis |

<table>
<tr><td>Vergleichsbedingung/-medikation</td><td>Not applicable</td></tr>
<tr><td>Gesamtzahl Patienten</td><td>Eleven evaluable patients were planned for the study with a maximum number of 13 patients allowed. Twelve patients were actually included. One patient was excluded for efficacy analysis after administration of Anti-Thymocyte-Globulins, interfering with Cyclophosphamide mechanism of action. All patients were considered for safety analysis.</td></tr>
<tr><td>Studienpopulation</td><td>All patients included in the study fulfilled the inclusion criteria.<br>No protocol deviations were recorded.<br>All patients were considered for safety analysis.<br>One patient (OCY-4) was excluded for efficacy analysis for the reasons given above.</td></tr>
<tr><td>Einschlusskriterien</td><td>– Patients with multiple myeloma, Non-Hodgkin’s lymphoma or Hodgkin’s disease after allogeneic stem cell transplantation with reduced intensity conditioning<br>– Written informed consent<br>– No uncontrolled infections</td></tr>
<tr><td>Ausschlusskriterien</td><td>– Severe organ dysfunction defined as:<br>– Cardiac left ventricular ejection fraction (LVEF) of less than 35%<br>– diffusing lung capacity (DLCO) of less than 40%<br>– total lung capacity (TLC) of less than 40%<br>– forced expiratory volume (FEV1) of less than 40%<br>– total bilirubin >3mg/dl<br>– creatinine-clearance of less than 40 ml/min<br>– pregnancy or breast feeding<br>– participation in other experimental drug trials</td></tr>
<tr><td>Darstellung der Demographie und Baseline-Charakteristika</td><td>Patient characteristics:
<table>
<tr><td>Median Age (yr)</td><td></td><td>47 (25-60)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Diagnosis</td><td>DLBCL</td><td>2 (18,2%)</td></tr>
<tr><td></td><td>T-NHL</td><td>2 (18,2%)</td></tr>
<tr><td></td><td>MM</td><td>2 (18,2%)</td></tr>
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|---|---|---|---|
| | HL | 2 (18,2%) |
| | MCL | 2 (18,2%) |
| | MZL | 1 (9%) |
| | | |
| **Prior therapies (Median)** | | 4 (2-9) |
| **Prior auto-SCT** | | 10 (91%) |
| **Auto to allo-SCT (Median days)** | | 375 (82-920) |
| | | |
| **Disease state pre-allo-SCT** | PR | 9 (82%) |
| | SD | 1 (9%) |
| | CR | 1 (9%) |
| | | |
| **Donor** | MRD | 6 (55%) |
| | MUD | 4 (36%) |
| | mMUD | 1 (9%) |
| | | |
| **Median CD34 dose (x$10^6$ /kg KG)** | | 4,9 (4,1-13) |

**<u>Darstellung</u>**

**Wirksamkeit**

All patients engrafted after stem cell transplantation. 3/11 patients remained free from GvHD and other immunosuppression. The primary endpoint was met.

**Clinical outcomes**

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| **Engraftment (Median days)** | Leukocyte | 18 (14-24) |
| | Neutrophils | 21 (17-33) |
| | Platelets | 18 (10-30) |
| | | |
| **Acute GvHD** | II-IV | 5 (45%) |
| | III-IV | 3 (27%) |
| **Time to aGvHD (Median days)** | | 32 (16-38) |
| | | |
| **Chronic GvHD** | NIH mild | 2 (1 post DLI) |
| **Time to cGvHD (Median days)** | | |
| | | |
| **NRM** | d+100 | 2 (18%) |
| | d+365 | 4 (36%) |
| **1yr-OS** | | 64% |
| **1yr-EFS** | | 55% |
| **Time to relapse (Median days)** | | 140 (77-511) |
| | | |
| **Follow-up (Median days)** | | 927 (348-1131) |

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| **Darstellung der**<br><br>**Sicherheit** | • Deaths (with time progression)<br><br>OCY-11: death due to **subarachnoidal hemorrhage** in thrombocytopenia on **d+29** after transplant<br><br>OCY-04: death due to **adenovirus and cytomegalovirus infection and lymphoma progression on d+54** after transplant<br><br>OCY-07: death due to **severe intestinal GvHD on d+91** after transplant<br><br>OCY-05: death due to severe intestinal and hepatic GvHD; additionally myloma progression shortly after transplant; **patient declined further treatment on d+105** after transplant and later on succumbed<br><br>OCY-06: death due to **sepsis on d+201** after transplant, patient compliance in doubt<br><br>OCY-09: death due to **relapse d+ 960** after transplant<br><br>• SAEs<br><br>List attached<br><br>Discussion of S(AE)s and deaths.<br><br>AEs reported were due to general toxicity of the transplant conditioning regimen. No unexpected events were suspected and no AE could be specifically attributed to the administration of cyclophosphamide, which, given pre-transplant, is part of many conditioning regimens. The incidence of grade 3 to 4 GvHD (27%) is higher than the usually expected 10-20% in the reduced-intensity transplant setting. This could be attributed to the omittance of continuous immunosuppression. However, a small sample size effect should also be considered for the discussion of these results. Moreover, also mismatched transplants (2 9/10 donors) were allowed in the protocol. Two of the deaths were in relation with the reported severe intestinal GvHD and a follow-up protocol will address this issue and implement short-term immunosuppression in addition to post-transplant cyclophosphamide. Mismatch transplants will not be allowed in the follow-up protocol. The engraftment of white and red blood cells as well as platelets was not prolonged. The subarachnoidal hemorrhage reported in one patient in thrombocytopenia is considered as incidental event. |
| **Statistische Methoden:** | • All patients recruited were considered for the safety analysis. For efficacy analyses, patients were not considered if they had not received the study medication or if efficacy of the concept of post-transplant cyclophos- |

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| | phamide had been considered impossible a priori<br>• Decription of the patient cohort (demography, underlying disease, prior treatment, transplantation), frequency/ median/ range<br>• Missing values were not imputed<br>• Due to the small sample size, there was no interim anal ysis, no ‚per-protocol'-analysis, no consideration of multiple testing, no subgroup analysis |


**SUMMARY**

Post-transplantation cyclophosphamide is feasible in the setting of peripheral blood stem cell transplantation following reduced-intensity conditioning in the non-haplo setting. Fast immune recovery and the chance of sparing continuous immunosuppression makes this approach attractive for conditions with high relapse risk. The beneficial effects of these properties have to be weighed against the potentially higher risk for severe acute GvHD, which may be associated with post-transplant cyclophosphamide in the context of peripheral blood transplants.

**Efficacy:**

Three patients remained free of any additional immunosuppression and the primary endpoint was reached. All patients engrafted and the median time to engraftment was 18, 21 and 18 days for leucocytes, neutrophils and platelets respectively. All patients developed complete donor chimerism in the bone marrow by day 30 after allo-SCT. Acute GvHD grade II-IV was reported in five of the patients (45%) and severe acute GvHD grade III-IV occurred in three patients (27%). Median time to onset of acute GvHD was 32 days with a range from 16 to 38 days. One patient developed chronic GvHD after cessation of immunosuppression following lymphoma relapse and one after DLI-administration for the treatment of lymphoma relapse (both de novo onset and NIH mild grade). Using competing risk analysis, the cumulative incidence of non-relapse mortality was 36% at one and two years after transplant. The cumulative incidence of relapse was 18% and 30% and the relapse-free survival was 45% at one and 34% at two years after transplant in this heavily pre-treated patient cohort.

**Safety**

The study treatment was generally well tolerated. AEs reported were due to general toxicity of the transplant conditioning regimen. No unexpected events were suspected and no AE could be specifically attributed to the administration of cyclophosphamide. The non-relapse mortality was higher than expected. This could be attributed to the higher incidence of severe GvHD. These data advise caution in the use of peripheral blood stem cells and single-agent GvHD prophylaxis with post-transplant cyclophosphamide. A follow-up protocol will address this issue and implement short-term immunosuppression in addition to post-transplant cyclophosphamide. Mismatch transplants will not be allowed in the follow-up protocol.

**Conclusion:**

In this clinical trial patients received post-transplant cyclophosphamide as single-agent, short-course GVHD prophylaxis. In Germany, peripheral blood stem cells are the most frequently used stem cell source. Therefore patients after peripheral blood stem cell transplantation were

included in the trial. In several studies, post-transplant cyclophosphamide has demonstrated strong efficacy as single-agent, short-course GVHD prophylaxis after bone marrow transplantation. Our small study suggests, that in peripheral blood transplants, a combination partner may be essential to mitigate the risk for severe acute GvHD in the early phase after transplant. Follow-up protocols will implement this knowledge. Despite the high non-relapse mortality, a relapse-free survival of 34% after two years in this high-risk patient cohort could be reported, potentially due to a reduced relapse rate. The beneficial effects post-transplant cyclophosphamide have to be weighed against the potentially higher risk for GvHD in the peripheral blood transplant setting.

**SAE Summary**

**OCY-04:**

Initial: (SAE No.1)

1) SAE-Term: respiratory failure with progressive lung infiltrates
2) SAE-Beschreibung: signs of sepsis, persistent CMV (?) –infection

Follow-up:

3) SAE-Term: respiratory failure with progressive lung infiltrates
4) SAE-Beschreibung: suspected intracranial bleeding, brain death

Bewertung:

5) death due to cerebral edema related to viral infection with CMV and Adenovirus

**OCY-05:**

Initial: (SAE No.1)

1) SAE-Term: GvHD Liver

Follow-up:

2) SAE-Term: GvHD Liver
3) SAE-Beschreibung: GvHD Liver; DD: toxic damage;

Initial: (SAE No.2)

1) SAE-Term: acute bleeding
2) SAE-Beschreibung: hemorrhagic diarrhea, suspected intestinal GvHD, anemia with hypotension

Bewertung.

3) severe upper intestinal bleeding due to two large ulceras

Follow-up:

4) SAE-Term: acute bleeding
5) SAE-Beschreibung: duodenal ulcera, recurrent bleeding, pneumonia, VZV-/Adenovirus-viremia, selflimiting VT

**OCY-06:**

Initial: (SAE No.1)

1) SAE-Term: Thrombopenia (prolonged hospitalisation due to)

**OCY-07:**

Initial: (SAE No.1)

1) SAE-Term: suspected intestinal GvHD (Hospitalization due to)

Bewertung:

2) Gut GvHD suspected

Follow-up:

3) SAE-Term: suspected intestinal GvHD now Sepsis
4) SAE-Beschreibung: Sepsis after intensified immunosuppression with tacrolimus+pentastatin

Follow-up:

5) SAE-Term: death in septic shock with pancytopenia with HSV-1-evidence in bone marrow

**OCY-09:**

Initial: (SAE No.1)

1) SAE-Term: suspected catheter-related thrombosis
2) SAE-Beschreibung: swelling left arm

Follow-up:

3) SAE-Term: suspected catheter-related thrombosis
4) SAE-Beschreibung: swelling left arm, no definite evidence of thrombosis

Initial: (SAE No.2)

1) SAE-Term: suspected pneumonia
2) SAE-Beschreibung: shortness of breath, leucopenia, fever

Follow-up:

3) SAE-Term: suspected pneumonia
4) SAE-Beschreibung: shortness of breath, leucopenia, fever, lobar pneumonia

**OCY-11:**

Initial: (SAE No.1)

SAE-Term: Subarachnoidal bleeding (Platetet count

13x1E9/L), Development of a cerebral edema with cerebral incarceration; life-threatining

Follow-up: Death

## SAE-Terms:

| | | |
|---|---|---|
| - Respiratory failure: | 1 | |
| - GvHD Liver: | 1 | |
| - Acute (intestinal) bleeding: | 1 | |
| - Thrombopenia: | 1 | |
| - Intestinal GvHD: | 1 | (2 mit Beschreibung) |
| - Sepsis (bzw. septic shock): | 1 | |
| - Pancytopenia: | 1 | |
| - Viremia: | 1 | (2 mit Beschreibung Infection) |
| - Catheter related thrombosis: | 1 | |
| - Pneumonia: | 1 | (2 mit Beschreibung) |
| - Subarachnoidal hemorrhage | 1 | |

## SAE-Beschreibung + Bewertung:

| | | |
|---|---|---|
| - Sepsis: | 1 | |
| - Infection (CMV, Adenovirus, VZV, HSV-1): | 1 | (2 mit Terms) |
| - Cerebral edema: | 1 | |
| - Intracranial bleeding | 1 | (suspected) |

| | | |
|---|---|---|
| - Toxic Liver damage: | 1 | |
| - Hemorrhagic diarrhea: | 1 | |
| - Intestinal GvHD: | 1 | (2 mit Terms) |
| - Anemia: | 1 | |
| - Hypotension: | 1 | |
| - Intestinal ulcera: | 1 | |
| - Pneumonia: | 1 | (2 mit Terms) |
| - Selflimiting VT: | 1 | |
| - Leucopenia: | 1 | |
| - Fever: | 1 | |
| - Subarachnoidal hemorrhage | 1 | |