NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

# Study Title:

Randomized phase-III study to compare two schedules of gemtuzumab ozogamicin as adjunct to intensive induction therapy and to compare intensive postremission therapy double blinded with or without glasdegib in adult patients with newly diagnosed AML.

**Short Title/ Acronym: GnG**

# Final Study Report

(acc to §42b AMG and §13(9) GCP-V)

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| **Version Number, Date:** | Version 1.0, Jan 31, 2023 |
| **Investigational product:** | Gemtuzumab ozogamicin infusion, (Mylotarg®,)<br>Glasdegib 100 mg/ 25 mg tablets (Daurismo®) |
| **Eudra-CT Number:** | 2019-003913-32 |
| **Protocol-Number:** | HeLeNe 18-02 |
| **ID Clinicaltrials.gov** | NCT04093505 |


**Sponsor:**

Ruprecht-Karls-University of Heidelberg
Medical Faculty represented in law by
Heidelberg University Hospital and its acting
Commercial Director Mrs. Katrin Erk
Im Neuenheimer Feld 672
D-69120 Heidelberg

**Coordinating / Principal Investigator:**

Prof. Dr. Richard F. Schlenk
NCT Trial Center
University Hospital Heidelberg
Im Neuenheimer Feld 130/3
D-69120 Heidelberg, Name

**Authors of Trial Report:**

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Dr. Markus Kratzmann & Dr. Lucian Le Cornet, NCT Trial Center,
University Hospital Heidelberg
Im Neuenheimer Feld 130/3
D-69120 Heidelberg


**Study Initiation and Completion Dates:**

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|---|---|
| FPFV/FPI | 31.03.2021 |
| LPFV/LPI | 02.05.2022 |
| LPLV/LPO | 09.09.2022 |
| EOS | 09.09.2022 |
| DBL | 12.12.2022 |

**CONFIDENTIAL**

## Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Report Version / Date: 20230131-GnG-Study Report_V1.0.docx

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|---|---|---|
| **Sponsor / or Designated Representatives (Reviewer)** | | Delegated to Coordinating Investigator |
| | Name | Place, Date |
| **Principal or Coordinating Investigator (Reviewer)** | Prof. Dr. Richard F. Schlenk | Heidelberg 31.01.2023 |
| | Name, Title | Place, Date |
| **Biostatistician (Authors)** | Lukas Baumann | Heidelberg, 31.01.2023 |
| | Name | Place, Date |

**Name of Sponsor/Company**:

Ruprecht-Karls-University of Heidelberg Medical Faculty represented in law by University Hospital Heidelberg and its acting Commercial Director Mrs. Katrin Erk

Im Neuenheimer Feld 672

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**Name of Finished Product**:

Mylotarg® (commercially available drug used)

(Daurismo® (clinical study supplies used)

**Name of Active Ingredient**:

Gemtuzumab ozogamicin (ATC-Code: L01XC05 )

Glasdegib (ATC-Code: L01XX63)

**Title of Study**:

Randomized phase-III study to compare two schedules of gemtuzumab ozogamicin as adjunct to intensive induction therapy and to compare intensive postremission therapy double blinded with or without glasdegib in adult patients with newly diagnosed AML.

**Acronym:** GnG

**Protocol versions:**

20201020_GnG Protocol V1_1.pdf (1st submission, approval BfArM Nov 18, 2020)

20210413 GnG Protocol V1_2.pdf (1st subst. amendment, approval BfArM May 21, 2021)

20210917 GnG Protocol V1_4.pdf (2nd subst. amendment, approval BfArM Sep 28, 2021)

20211215 GnG Protocol V1_5.pdf (3rd subst. amendment, approval BfArM Jan 21, 2022)

**Study Center(s) and Principal Investigator(s)**:

A list of study centers including names of principal Investigators is given in Appendix 1.

**Publication (Reference)**:

Jaramillo S, Krisam J, Le Cornet L et al. Rationale and design of the 2 by 2 factorial design GnG-trial: a randomized phase-III study to compare two schedules of gemtuzumab ozogamicin as adjunct to intensive induction therapy and to compare double-blinded intensive postremission therapy with or without glasdegib in older patients with newly diagnosed AML. Trials. 2021; 22: 765; published online 2021 Nov 3. doi: 10.1186/s13063-021-05703-w

| **Studied Period (years)**: | | **Phase of Development**: |
|---|---|---|
| Date of first enrollment (FPI): | 31.03.2021 | Phase III |
| Date of last enrollment (LPI): | 02.05.2022 | |
| Date notification (to BfArM & EC) of premature stop of patient recruitment: | 09.05.2022 | |
| Date of last patient out (LPO): | 09.09.2022 | |

**Objectives**:

The study was planned to address two primary objectives:

- To assess clinical efficacy of sequential (denoted as GO-147) or one-dose (denoted as GO-1) gemtuzumab ozogamicin as adjunct to induction therapy in older patients with newly diagnosed AML; clinical efficacy determined by minimal residual disease (MRD) negativity after induction therapy.
- To assess clinical efficacy of glasdegib as adjunct to 2 months consolidation and as single agent 6 months maintenance therapy in older patients with newly diagnosed AML.

Since the trial was prematurely terminated not all objectives of the trial could be addressed. 26 patients were randomized to treatment (1 of them was never treated) and 13 received consolidation therapy within the trial. Efficacy was evaluated descriptively for the first comparison, i.e. GO-1 vs. GO-147.

**Methodology**:

The GnG study was designed as a multicenter, randomized phase III trial with MRD-negativity after induction therapy and event-free survival as primary endpoints. The two research questions were planned to be addressed in a 2 by 2 factorial design. Patients were upfront randomized for the two induction schedules (GO-147 versus GO-1) and for glasdegib or placebo (double blinded) as adjunct to consolidation therapy and as single agent 6 months maintenance therapy in a 1:1:1:1 ratio.

With the approval of oral azacitidine (Onureg®) as maintenance therapy in adult patients with acute myeloid leukemia (AML) in May 2021, the administration of placebo was ethically no longer justifiable for the targeted patient population. Hence, the concept of double-blinded treatment with glasdegib or placebo has been repealed by the 2nd substantial amendment (see above). Moreover, all patients entering the consolidation phase were offered the opportunity to switch to oral azacitidine instead of continuing with glasdegib.

After the inclusion of 30 patients, patient recruitment was stopped prematurely (see above). The unexpectedly slow recruitment rate until May 2022 made it obvious that the planned sample size was unachievable within a reasonable timeframe.

**Number of Patients (planned and analyzed)**:

The total planned sample size was 252, patient recruitment was stopped after the inclusion of 30 patients. Of these, 26 patients were randomized to treatment, but one of the randomized patients did never receive treatment.
The applicable patient analysis sets are described below (see statistical methods).

**Diagnosis and Main Criteria for Inclusion**:

Newly diagnosed CD33 positive acute myeloid leukemia, age ≥18 (original age at inclusion was ≥60 years, subsequent adjustment of age at inclusion was implemented via 2nd and 3rd substantial amendments, see above) no prior chemotherapy for leukemia (except hydroxyurea ≤7 days), availability of central genetic and immunophenotypic assessment, ECOG PS ≤2, effective contraception

**Investigational Product, Dose And Mode Of Administration, Batch Numbers**:

- Gemtuzumab ozogamicin (INN), Drug Code PF-05208747, ATC Code L01XC05, 20 mL ampoules of 5 mg (Mylotarg®, commercially available drug used), powder for intravenous administration, manufacturer Pfizer Pharma GmbH.
  Batch Number: AP3995
- Glasdegib (INN), Drug Code PF- 04449913, ATC Code L01XX63, tablets of 100 mg and 25 mg (Daurismo®, clinical study supplies used), oral administration, manufacturer Pfizer Pharma GmbH.
  Batch Numbers: GnG25/202114, GnG100/202114

**Planned Duration of Treatment**:

Planned overall duration of treatment per patient was approximately 9 months, consisting of a 4-week induction therapy cycle (plus a 4-week salvage therapy cycle if needed), two 4-week consolidation therapy cycles and up to six 4-week maintenance therapy cycles.

**Reference Therapy, Dose and Mode of Administration, Batch Numbers**:

Placebo matching glasdegib, tablets of 100 mg and 25 mg, oral administration, manufacturer Pfizer Pharma GmbH.

Batch Numbers: GnG25/202114, GnG100/202114

**Criteria for Evaluation**:

Due to the premature study termination, study endpoints were not evaluable as planned per protocol.

**Efficacy**:

With respect to the comparison between GO-1 and GO-147 evaluated efficacy endpoints were the following (only of exploratory nature due to the low sample size, n=25):

Primary endpoints

- Short-term: MRD-negativity, defined as absence of leukemic cells at the end of the induction therapy assessed by flow-cytometry (patients receiving salvage therapy, any-cause of death before MRD measurement and treatment discontinuation with no response in the last assessment regarded as MRD-positive).
- Long-term: EFS, defined as the time from randomization to time until one of the following events, whichever occurs first: a) failure to obtain CR/CRi after induction therapy (includes cases with necessary salvage therapy and treatment discontinuation with no response in the last assessment), b) relapse from CR/CRi for patients with induction success or c) death from any cause.
  In case of no CR or no CRi after induction therapy event-time is set to 28 days.

Secondary endpoints

- CRR, defined as the proportion of patients experiencing CR/CRi after induction therapy (any-cause death before CR/CRi measurement, patients achieving CR/CRi only after salvage therapy and treatment discontinuation with no response in the last assessment regarded as failure to obtain CR/CRi).
- RFS, defined as the time from achievement of CR/CRi after randomization to time of recurrence of the disease or death from any cause, whatever occurs first.
- OS, defined as the time from randomization to time of death from any cause.

Consolidation therapy was initiated in 13 patients only, efficacy endpoints related to treatment with Glasdegib were not evaluated.

**Safety:**

The safety evaluation is primarily based on adverse event data. Laboratory data were evaluable to only a very limited extent.

**Statistical methods**:

The number of 26 randomized (thereof 25 evaluable) patients is far below the planned number of 252; data collected in this trial is not suitable to answer the trial objectives and allows only a descriptive analysis.

With respect to study endpoints see above (Criteria for Evaluation).

Analysis Sets:

- The Full Analysis Set (FAS) includes all randomized patients with treatment groups assigned in accordance with the randomization, regardless of the treatment actually received. The FAS is the primary analysis population for primary and secondary efficacy endpoints. Patients randomized but not receiving study treatment are excluded from the FAS (modified ITT).
- The Safety Set is the primary population for the evaluation of all safety endpoints and comprises all patients enrolled who received at least one dose of study medication. Patients are analyzed according to the treatment actually received. No treatment switch occured before end of treatment, therefore the safety set is identical to the FAS.

Withdrawals and Missing Data:

All patients randomized have consented to the use of their data for the analysis. Excluded were only data of patients having subsequently withdrawn explicitly his/her consent to the use of their data. For all time-to-event endpoints patients who dropped out or who have an incomplete follow-up or no event at the end of the follow-up period are censored at the date of their last follow-up. For all non-time-to-event endpoints no imputation of missing data is conducted and the analysis is based on all complete cases.

Descriptive Methods:

Disposition of patients (numbers of patients randomized per group, assessed for eligibility excluded from analysis sets etc.) is presented via a CONSORT flow diagram (Appendix 2).

Continuous variables are described using number of observations, mean, standard deviation, median, Q1, Q3, minimum, maximum and number of non-missing values. For categorical variables, absolute and relative frequencies are given with missing values reported as separate category.

Analysis of efficacy endpoints (FAS used for all analyses):

The short-term primary endpoint MRD-negativity is analyzed using a descriptive chi-square test. A 95% confidence interval (CI) for the rate difference is calculated.

EFS and the secondary time-to event endpoints (OS, RFS) are analyzed by descriptive log-rank tests and Kaplan-Meier estimators.

CRR is analyzed analogously to the primary short-term endpoint, using a descriptive chi-square test and calculating a 95% CI for the rate difference.

Analysis of safety endpoints (safety set used for all analyses):

AEs are summarized by number and percentage of patients having any AE or SAE, and having each individual type of AE, and by determination of the maximum individual toxicity grade (over all forms of toxicity) for each treatment cycle. Most common AEs are also determined. Laboratory data are summarized presenting summary statistics of raw data. Incidence rates for the occurrence of any AE/SAE are summarized along with two-sided 95% CIs for the rate difference and analyzed by (descriptive) chi-squared tests.

**SUMMARY - CONCLUSIONS**

**EFFICACY RESULTS**:

Due to the small number of patients randomized (n=26) and finally treated (n=25), no robust analyses concerning efficacy were possible. Based on descriptive analysis for the randomization of GO-1 versus GO-147 the numerical value of MRD negativity after induction therapy was higher in the GO-147 arm with 75.0% (9/12) compared to 45.5% (5/11). This higher rate of MRD negativity after induction therapy also translated in a numerically better event free survival. Only 13 patients received consolidation therapy within the trial. Therefore, efficacy was only evaluated for the first comparison, i.e. GO-1 vs. GO-147. Based on the short follow-up, analyses of the endpoints relapse-free survival and overall survival were not expected to render robust results and not evaluated here.

**SAFETY RESULTS**:

With respect to the induction phase, the number of patients experiencing at least one or more adverse events was overall 96% (24/25) with no difference between treatment arms GO-1 and GO-147. The number of patients experiencing one or more serious adverse events was overall 52% (13/25). Toxicity rates were numerically higher in the GO-147 arm with a cumulative percentage of SAEs of 61.5% (8/13) compared to 41.7% (5/12) in the GO-1 arm.

During the observation period of the consolidation and maintenance phase rates of occurrence of AEs were 85.7% (6/7) in the placebo and 100% in the glasdegib arm (6/6), respectively. Corresponding figures for SAEs were 14.3% (1/7) in the placebo and 66.7% (4/6) in the glasdegib arm.

The spectrum and frequency of AEs as well as SAEs were in the expected range.

**CONCLUSION**:

Due to the premature termination of the trial after only n=26 being randomized, no conclusion could be drawn. However, the initial hypothesis that treatment during induction therapy with GO-147 results in a higher rate of MRD negativity compared to GO-1 is at least numerically supported.

**Substantial Amendments / Interruptions or Early Termination**:

Notification of recruitment stop May 05, 2022, early termination of study Sep 09, 2022; recruitment goal turned out unachievable.

**Version / Date of Report**: 20230131-GnG-Study Report_V1.0-upload.docx

**Appendices**

Appendix 1 – List of Study Centers

Appendix 2 – Patient Disposition (CONSORT Flow Diagram)

Appendix 3 – Abbreviations

## Appendix 1 – List of Study Centers

Center No. 01: Universitätsklinikum Heidelberg, Innere Medizin V, Im Neuenheimer Feld 410, 69120 Heidelberg; Investigator Prof. Dr. Richard F. Schlenk

Center No. 02: Universitätsklinikum Aachen, AöR, Medizinische Klinik IV, Pauwelsstraße 30, 52074 Aachen; Investigator Dr. med. Martina Crysandt

Center No. 03: Klinikum Augsburg II. Medizinische Klinik, Stenglinstraße 2, 86156 Augsburg; Investigator PD Dr. Andreas Rank

Center No. 04: Augusta Kranken Anstalt, Klinik für Hämatologie, Onkologie & Palliativmedizin, Bergstr. 26, 44791 Bochum; Investigator Prof. Dirk Behringer

Center No. 05: Universitätsklinikum Bonn, Medizinische Klinik und Poliklinik III, Venusberg – Campus 1, 53127 Bonn; Investigator Dr. med. Lino Teichmann

Center No. 06: Städtisches Klinikum Bielefeld, Klinik für Hämatologie, Onkologie und Palliativmedizin, Teutoburger Str. 50, 33604 Bielefeld; Investigator PD Dr. med. Martin Görner

Center No. 07: Evangelische Diakonie Krankenhaus, Medizinische Klinik II, Gröpelinger Heerstr. 406-408, 28239 Bremen; Investigator Prof. Dr. med. Ralf Ulrich Trappe

Center No. 08: Universitätsklinikum Carl Gustav Carus Dresden, Medizinische Klinik und Poliklinik I, Fetscherstr. 74, 1307 Dresden; Investigator Prof. Dr. med. Christoph Röllig

Center No. 09: Universitätsklinikum Erlangen, Medizinische Klinik 5, Ulmenweg 18, 91054 Erlangen; Investigator Prof. Dr. med. Stefan W. Krause

Center No. 10: Universitätsklinikum Essen, Klinik für Hämatologie, Hufelandstr. 55, 45122 Essen; Investigator Dr. med. Maher Hanoun

Center No. 11: Klinikum Frankfurt (Oder), Medizinische Klinik I, Müllroser Chaussee 7, 15236 Frankfurt (Oder); Investigator Dr. med. Olaf Hopfer

Center No. 12: Klinikum Kaiserslautern, Innere Medizin I, Hellmut-Hartert-Straße 1, 67655 Kaiserslautern; Investigator Prof. Dr. med. Gerhard Held

Center No. 13: Städtisches Krankenhaus Kiel, 2. Medizinische Klinik, Chemnitzstr. 33, 24116 Kiel; Investigator Dr. med. Sebatian Buske

Center No. 14: Universitätsklinikum Schleswig-Holstein, Klinik für Innere Medizin II Universitätsklinikum Schleswig-Holstein, Arnold-Heller-Straße 3, Haus 50, 24105 Kiel; Investigator Dr. med. Lars Fransecky

Center No. 15: Universitätsklinikum Leipzig, Medizinische Klinik I – Hämatologie und Zelltherapie, Liebigstraße 22, 4103 Leipzig; Investigator PD Dr. med. Sabine Kayser

Center No. 16: Universitätsklinikum Münster, Medizinische Klinik A, Albert-Schweitzer-Campus 1 Gebäude A1, 48149 Münster; Investigator Prof. Dr. med. Christoph Schliemann

Center No. 17: Klinikum Nürnberg Nord, Klinik für Innere Medizin V, Prof.-Ernst-Nathan-Str. 1, 90419 Nürnberg, Investigator Dr. med. Kerstin Schaefer-Eckart

Center No. 18: Brüderkrankenhaus St. Josef Paderborn, Klinik für Hämatologie und Onkologie, Husener Str. 46, 33098 Paderborn; Investigator Dr. med. Tobias Gaska

Center No. 19: Elblandkliniken Stiftung & Co.KG, Klinik für Innere Medizin II, Weinbergstraße 8, 1589 Riesa; Investigator Prof. Dr. med. Jörg Schubert

Center No. 20: Diakoneo - Klinikum Schwäbisch Hall, Innere Medizin III, Stammhaustr 8, 74523 Schwäbisch Hall; Investigator Dr. med. Thomas Geer

Center No. 21: Robert-Bosch-Krankenhaus Stuttgart, Hämatologie, Onkologie und Palliativmedizin, Auerbachstraße 110, 70376 Stuttgart; Investigator Dr. med. Martin Kaufmann

Center No. 22: Klinikum Wiesbaden, Innere Medizin III, Ludwig-Erhard-Str. 100, 65199 Wiesbaden; Investigator Dr. med. Arne Brecht

Center No. 23: Ev. Stift St. Martin Koblenz, IM Studienzentrum, Koblenzer-Str. 115-155, 56073 Koblenz; Investigator Dr. med. Dirk Niemann

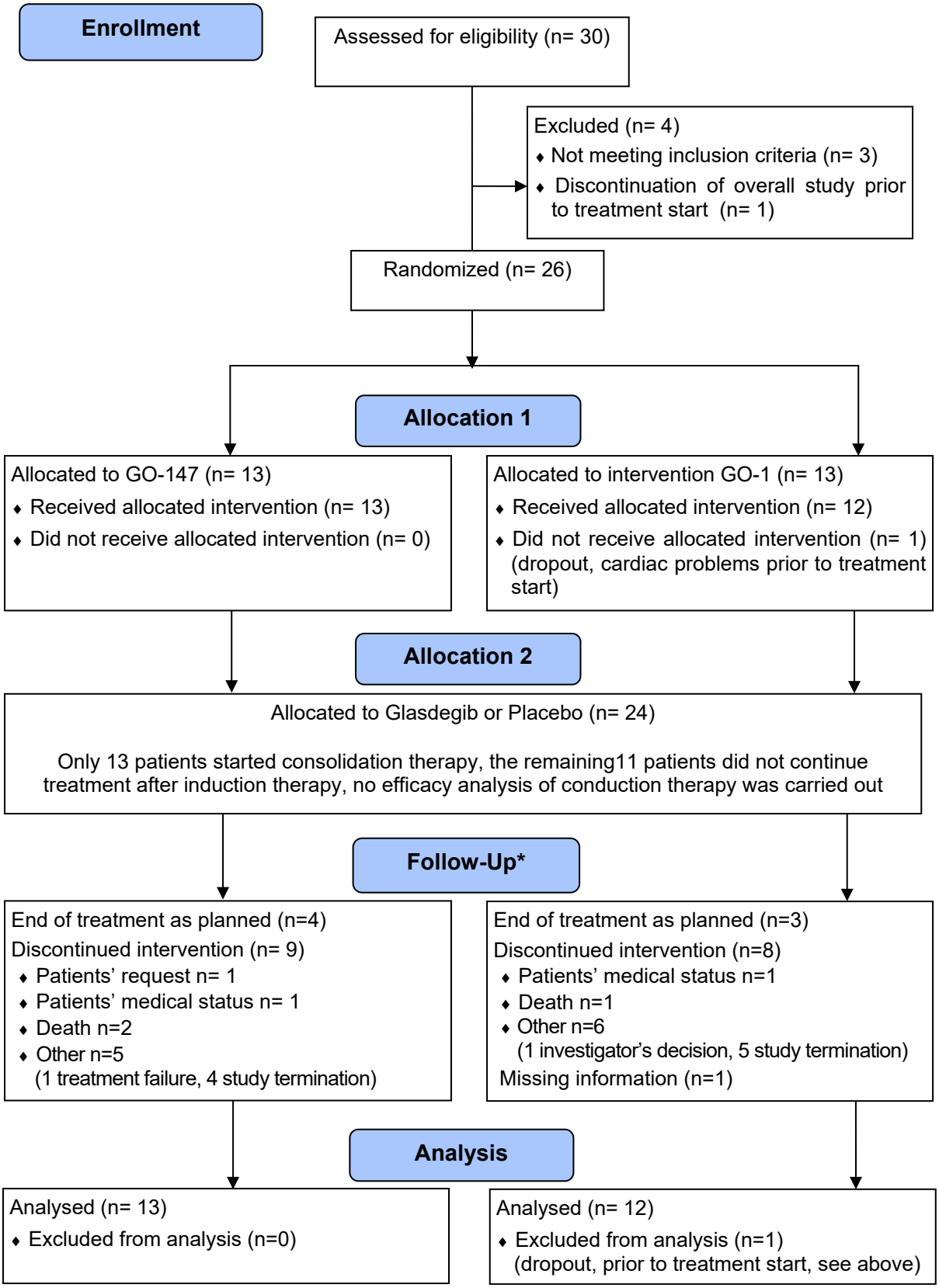
Center No. 24: Sozialstiftung Bamberg, Medizinische Klinik V, Hämatologie und Internistische Onkologie, Buger Straße 80, 96049 Bamberg; Investigator Dr. med. Matthias Herrmann

Center No. 25: Klinikum Winnenden, Hämatologie, Onkologie und Palliativmedizin, Am Jakobsweg 1, 71364 Winnenden; Investigator Prof. Dr. med. Schaich

Center No. 26: Kliniken Maria Hilf GmbH, Medizinischen Klinik I, Viersener Straße 450, 41063 Moenchengladbach; Investigator Prof. Dr. med. Ulrich Graeven

Center No. 27: Rotkreuzklinikum München, Abteilung für Innere Medizin III – Hämatologie und Onkologie, Nymphenburger Straße 163, 80637 München; Investigator PD Dr. med. Alexander Hoellein

## Appendix 2 – Disposition of Patients (CONSORT Flow Diagram)




*Follow-up reports refer to the period until End of Treatment

## Appendix 3 – Abbreviations

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|---|---|
| AE | Adverse Event |
| AML | Acute Myeloid Leukemia |
| ATC | Anatomical Therapeutic Chemical Code |
| BfArM | Bundesinstitut für Arzneimittel und Medizinprodukte<br>(Federal Institute for Drugs and Medical Devices, Germany) |
| CI | Confidence Interval |
| CR | Complete Remission |
| CRi | Complete Remission with incomplete hematological recovery |
| CRR | Complete Remission Rate |
| DBL | Database Lock |
| EC | Ethics Committee |
| EFS | Event-free Survival |
| ECOG PS | Eastern Cooperative Oncology Group performance status |
| EOS | End of Study |
| EOT | End of Treatment |
| FAS | Full Analysis Set |
| FPFV | First Patient First Visit |
| FPI | First Patient In |
| GO-1 | Gemtuzumab ozogamicin, 1 dose |
| GO-147. | Gemtuzumab ozogamicin, 3 doses (days 1, 4, 7) |
| INN | International Nonproprietary Name |
| ITT | Intention To Treat |
| LPFV | Last Patient First Visit |
| LPI | last Patient In |
| LPFV | Last Patient First Visit |
| LPI | last Patient In |
| LPLV | Last Patient Last Visit |
| LPO | Last Patient Out |
| MRD | Measurable Residual Disease |
| OS | Overall Survival |
| RFS | Relapse-free Survival |
| SAE | Serious Adverse Event |