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

GnG

Protocol Code:	HeLeNe-18-02
EudraCT No.:	2019-003913-32
Clinicaltrials.gov:	NCT04093505
Clinical Phase:	Therapeutic confirmatory (Phase III)
Date and Version:	20211215 GnG Protocol V1_5
Sponsor:	Ruprecht-Karls-University of Heidelberg Medical Faculty represented in law by Universitätsklinikum Heidelberg and its acting Commercial Director Mrs. Katrin Erk Im Neuenheimer Feld 672 D-69120 Heidelberg

Responsibilities

Coordinating Investigator *
Prof. Dr. Richard F. Schlenk
NCT Trial Center
University Hospital Heidelberg
Im Neuenheimer Feld 130/3
D-69120 Heidelberg
Phone: +49 (0)6221 56 6228
Fax: +49 (0)6221 56 5863
E-mail: richard.schlenk@nct-heidelberg.de
* LKP According to § 40 German Drug Law (AMG) and sponsor representative

Joint Coordinating Investigator
Prof. Dr. Carsten Müller-Tidow
Department of Internal Medicine V
University Hospital Heidelberg
Im Neuenheimer Feld 410
D-69120 Heidelberg
Phone: +49 (0)6221 56 8000
Fax: +49 (0)6221 56 5813
E-Mail: direktor.med5@med.uni-heidelberg.de

Trial Statistician
Dr. Johannes Krisam
Institute of Medical Biometry
University Hospital Heidelberg
Im Neuenheimer Feld 130/3
D-69120 Heidelberg
Phone: +49 (0)6221 56 32630
Fax: +49 (0)6221 56 4195
E-mail: krisam@imbi.uni-heidelberg.de

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
Phone: +49 (0)6221 56 7002
Fax: +49 (0)6221 56 4888
E-mail: Kaufmaennische-Direktion@med.uni-heidelberg.de

Supervising Statistician
Prof. Dr. Meinhard Kieser
Institute of Medical Biometry and Informatics
University Hospital Heidelberg
Im Neuenheimer Feld 130/3
D-69120 Heidelberg
Phone: +49 (0)6221 56 4140
Fax: +49 (0)6221 56 4195
E-mail: meinhard.kieser@imbi.uni-heidelberg.de

Trial Coordination
Dr. Markus Kratzmann
Dr. Lucian Le Cornet
NCT Trial Center
National Center for Tumor Diseases (NCT)
Im Neuenheimer Feld 130.3
69120 Heidelberg, Germany
Phone: +49 (0)6221 / 56-4183/ -6553
Fax: +49 (0)6221 / 56-5863
E-Mail: GnG@nct-heidelberg.de

Monitoring
KKS Heidelberg
University Hospital Heidelberg
Im Neuenheimer Feld 130/3,
D-69120 Heidelberg
Phone: +49 (0)6221 56 34500
Fax: +49 (0)6221 56 1331
E-Mail:. Karsten.Thelen@med.uni-heidelberg.de

Medical Coordination
Dr. Sonia Jaramillo
Department of Internal Medicine V
University Hospital Heidelberg
Im Neuenheimer Feld 410
D-69120 Heidelberg
Phone: +49 (0)6221 56 38081
Fax: +49 (0)6221 56 5863
E-mail: Sonia.Jaramillosegura@med.uni-heidelberg.de

Data Management
Frau Olga Eissymont
Institute of Medical Biometry
Heidelberg University Hospital
Im Neuenheimer Feld 130.3
D-69120 Heidelberg
Phone: +49 (0)6221 56 37580
Fax: +49 (0)6221 56 4195
E-mail: eissymont@imbi.uni-heidelberg.de

Pharmacovigilance
KKS Heidelberg
University Hospital Heidelberg
Im Neuenheimer Feld 130/3,
D-69120 Heidelberg
Phone: +49 (0)6221 56 34500
Fax: +49 (0)6221 56 1331
E-Mail: Jacek.Hajda@med.uni-heidelberg.de

SAE-Reporting:
Fax: +49 (0)6221 56 33687
E-Mail: pharmakovigilanz.KKS@med.uni-heidelberg.de

Central molecular genetics and MRD Laboratory
Dr. Katharina Kriegsmann
PD Dr. med. Michael Hundemer
Hematological diagnostic laboratory
Department of Internal Medicine V
Im Neuenheimer Feld 410 / Room 01.136
D-69120 Heidelberg
Phone: +49 (0)6221 56 36995
Fax: +49 (0)6221 56 - 8588
E-Mail: Katharina.Kriegsmann@med.uni-heidelberg.de

Quality of Life / Patient-Reported Outcomes
Prof. Dr. Karen Steindorf
Division of Physical Activity, Prevention and Cancer
German Cancer Research Center
Im Neuenheimer Feld 460
D-69120 Heidelberg
Phone: +49 (0)6221 42 2351
E-Mail: k.steindorf@dkfz.de

Pharmacy
Pharmacy of the University Hospital Heidelberg
Im Neuenheimer Feld 670
D-69120 Heidelberg
Phone: +49 (0)6221 56 6763

Health Economic Evaluation
Prof. Dr. Michael Schlander
Division of Health Economics
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
Phone: +49 (0)6221 42 1910
E-Mail: m.schlander@dkfz.de

Summary

Overall survival remains poor in patients with acute myeloid leukemia (AML). Approximately half of the younger (≤60 years) patients and about 80-90% of the older patients still relapse despite intensive consolidation therapy, and the majority of relapsed patients succumb to their disease.. Castaigne et al. were able to show a significant improvement in event-free, relapse-free and overall survival but not complete remission rate by adding gemtuzumab ozogamicin (GO) to intensive induction therapy. The benefit of GO was associated with significantly reduced measurable residual disease (MRD) after induction therapy and thus MRD may serve as a surrogate endpoint. Although now approved, the optimal dosage of GO in combination with intensive induction therapy is not yet defined. No clear differences were identified in a recently published meta-analysis including trials with fractionated GO 3 mg/m² on days 1, 4, and 7 (GO-147) and GO (3 mg/m² or 6 mg/m²) given once (GO-1). Thus the first research question of this study is whether GO-147 outperforms GO-1 in induction therapy with the endpoint MRD status after induction therapy.

The small molecule inhibitor of smoothened (SMOi), glasdegib, is able to attenuate the leukemia-initiation potential of AML-cells in serial transplantation mouse models. In a phase-I study it has been shown, that glasdegib can be safely administered in newly diagnosed AML patients in a dose of 400 mg p.o. daily, the recommended phase-II dose was given with 200 mg per day or lower. Main side-effects were dysgeusia, decreased appetite, and alopecia. In a randomized phase-II study older patients not eligible for intensive chemotherapy had a significantly better overall survival when treated with low-dose cytarabine plus glasdegib compared to low-dose cytarabine alone. Most interestingly, the survival benefit was not only attributable to a significantly higher complete remission (CR) rate but also in maintaining an anti-leukemic efficacy of glasdegib over time in CR but also in no-CR patients. Based on the observation that despite intensive consolidation therapy still most of older AML-patients relapse and die of their disease, the second research question is whether the addition of glasdegib added to consolidation followed by single agent 6-months maintenance therapy (with an optional switch to standard of care according to Physician's Choice during maintenance) improves event-free survival. Both research questions are addressed by an up-front randomized comparison using a 2 by 2 factorial design.

Zusammenfassung

Patienten mit akuter myeloischer Leukämie haben weiterhin ein schlechtes Gesamtüberleben. Ungefähr die Hälfte der jüngeren Patienten (≤60 Jahre) und 80-90% der älteren Patienten werden trotz intensiver Konsilidierungstherapie rückfällig. Die Mehrzahl davon verstirbt an der Erkrankung. Castaigne et al. konnten durch die zusätzliche Gabe von Gemtuzumab-Ozogamicin (GO) zur intensiven Induktionstherapie eine signifikante Verbesserung der ereignis- und rezidivfreien Überlebensrate und Gesamtüberlebensrate, jedoch nicht der vollständigen Remission, erreichen. Der Nutzen von GO ging mit einer signifikant verringerten messbaren Resterkrankung (MRD) nach Induktionstherapie einher, weshalb MRD als Surrogatendpunkt dienen kann. Trotz Zulassung durch die Behörden, ist die optimale Dosierung von GO in Kombination mit einer intensiven Induktionstherapie noch nicht klar definiert. In einer großen Metaanalyse zu GO in der Induktionstherapie wurden eine Studie mit fraktioniertem Einsatz von GO (GO 3 mg/m² an den Tagen 1, 4 und 7 (GO-147)) und verschiedenen Studien mit einmaliger Gabe von GO (3 mg/m² oder 6 mg/m²) untersucht, ohne dabei zwischen beiden Applikationsarten klare Unterschiede darstellen zu können. Basierend auf diesen Daten ist die erste Forschungsfrage in der GnG Studie, ob GO-147 im Vergleich zu GO-1 in der Induktionstherapie in Bezug auf den Endpunkt MRD-Status nach der Induktionstherapie überlegen ist.

Mausmodelle mit serieller Transplantation haben gezeigt, dass der niedermolekulare Inhibitor von Smoothened (SMOi), Glasdegib, in der Lage ist das Leukämie-initiierende Potential von AML-Zellen zu reduzieren.

In einer Phase-I-Studie wurde gezeigt, dass Glasdegib bei neu diagnostizierten AML-Patienten in einer Dosis von 400 mg p.o. täglich sicher verabreicht werden kann, die empfohlene Phase-II-Dosis wurde mit 200 mg pro Tag definiert. Hauptnebenwirkungen waren Dysgeusie, verminderter Appetit und Alopezie. In einer randomisierten Phase-II-Studie bei älteren Patienten, die nicht für eine intensive Chemotherapie in Frage kamen, war die Kombination von Glasdegib und Cytarabine der alleinigen Cytarabintherapie deutlich überlegen. Interessanterweise war der Überlebensvorteil nicht nur auf eine signifikant höhere Rate kompletter Remission (CR) zurückzuführen, sondern auch auf eine anti-leukämischen Wirksamkeit von Glasdegib im Behandlungsverlauf bei Patienten mit aber auch ohne CR.

Basierend auf der Beobachtung, dass trotz intensiver Konsolidierungstherapie die meisten älteren AML-Patienten rezidivieren und an ihrer Krankheit sterben, ist die zweite Forschungsfrage, ob die Zugabe von Glasdegib zur Konsolidierung, gefolgt von einer 6-monatigen Erhaltungstherapie mit Glasdegib (mit der Option während der Erhaltungsphase zur zugelassenen Standardtherapie zu wechseln), das ereignisfreie Überleben verbessert. Die zwei Forschungsfragen werden in einem 2×2 faktoriellen Studiendesign untersucht.

Table of Contents

Protocol Synopsis

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.

Phase

Phase III

Sponsor

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

Coordinating Investigator (LKP)

Prof. Dr. Richard F. Schlenk

Financing/ Status of the Sponsor

The trial is co-financed by funds of University hospital of Heidelberg and Pfizer GmbH.
Study drugs are provided free of charge by Pfizer GmbH.

Indication

Acute myeloid leukemia according to WHO 2016 classification

Trial Population - Inclusion Criteria

- Patients with newly diagnosed CD33 positive acute myeloid leukemia according to the 2016 WHO classification
- Genetic and immunophenotypic assessment in the central laboratory
- No prior chemotherapy for leukemia except hydroxyurea to control hyperleukocytosis (≤7 days) *
- Age ≥18 years, no upper age limit
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2. See appendix 19.1
- Signed written informed consent
- Ability of patient to understand character and consequences of the clinical trial
- Non-pregnant and non-nursing women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 72 hours prior to start of study treatment. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
  Post-menopausal** or evidence of non-childbearing status is defined within this clinical trial:
  - Amenorrheic for at least **24 consecutive months** without an alternative medical cause following cessation of exogenous hormonal treatments.
  - Chemotherapy-induced menopause with >1 year interval since last menses
  - Surgical sterilisation

- WOCBP are to be advised using two effective methods of birth control to avoid pregnancy throughout the study and for at least 7 months after the last dose of GO. This includes effective contraception methods that can achieve a failure rate of less than 1% per year (e.g. hormonal contraceptive and condom, IUD/IUS and condom) or sterilization, resulting in a failure rate less than 1% per year.
- Fertile men must be willing and able to use two effective methods of birth control (e.g. latex condoms plus hormonal contraception in their partner) throughout the study and for at least 4 months after the last dose of GO, if their sexual partners are WOCBP (acceptable methods see above). A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
- For WOCBP and fertile men equally, effective contraception methods are also required during the intake of glasdegib and for at least 30 days thereafter.

* in case hyperleukocytosis is not controllable with hydroxyurea treatment with cytarabine should be discussed with the principal investigator or medical coordinator.

** A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy at investigator's discretion.

Trial Population - Exclusion Criteria

- AML with *PML-RARA* or *BCR-ABL1*
- Patients with known active central nervous system (CNS) leukemia (assessed clinically).
- Prior treatment with a smoothened inhibitor (SMOi) and/or hypomethylating agent (HMA) for AML. (treatment of a preceding myelodysplastic syndrome (MDS) with HMA is not an exclusion criterion.)
- Inadequate renal function: creatinine >1.5 x upper normal serum level; estimated creatinine clearance ≤30 mL/min (calculated using the standard method for the institution).
- Inadequate liver function: ALT and AST ≥2.5 x ULN), total bilirubin ≥1.5 x ULN; Alkaline phosphatase ≥2.5 x ULN. Known liver cirrhosis or history of sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD)
- Uncontrolled hypertension; severe obstructive or restrictive ventilation disorder
- Any one of the following ongoing or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia), right or left bundle branch block and bifascicular block, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF NYHA III/IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism; as well as bradycardia defined as <50 bpms
- QTc interval >470 msec using the Fridericia correction (QTcF).
- Uncontrolled infection
- Prior allogeneic hematopoietic stem cell transplantation (Allo-HCT) for the treatment of a condition different from AML
- Patients known to be refractory to platelet or packed red cell transfusions as per institutional guidelines, or who are known to refuse or who are likely to refuse blood product support.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancer or low grade prostate carcinoma, where an active surveillance is foreseen (Gleason Score 6, normal rectal examination, PSA <10, ≤2 positive biopsies out of 12, and less than 50% of tumorinfiltration on the examined sample). Patients are not considered to have a "currently active" malignancy if they have completed therapy for more than one year and are considered by their physician to be at less than 30% risk of relapse within one year.

- Severe neurologic or psychiatric disorder interfering with ability of giving informed consent
- Known or suspected active alcohol or drug abuse
- Known positivity for human immunodeficiency virus (HIV), active hepatitis B virus (HBV), hepatitis C virus (HCV), or hepatitis A infection
- Evidence or history of severe non-leukemia associated bleeding diathesis or coagulopathy
- Major surgery within four weeks prior to enrolment
- No consent for biobanking and for registration, storage and processing of the individual disease-characteristics and course as well as information of the family physician about study participation.
- Pregnancy and lactation
- History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product
- Participation in a clinical study involving an investigational drug(s) (Phases 1-4) within 4 weeks prior to study entry.

Objectives

The primary objectives are

- To assess clinical efficacy of sequential or one-dose gemtuzumab ozogamicin as adjunct to induction therapy in adult patients with newly diagnosed AML. Clinical efficacy is determined by 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, with an optional switch to standard of care (SOC) according to Physician's Choice during maintenance (SOC^{PhC}), in older patients with newly diagnosed AML. Clinical efficacy is determined by event-free survival (EFS) defined as the time from randomization to time until one of the following events, whichever occurs first: a) failure to obtain complete remission (CR) or complete remission with incomplete hematological recovery (CRi), b) relapse from CR/CRi for patients with induction success or c) death from any cause. Patients without an applicable event are censored on the last date of follow-up.

The **secondary objectives are**

- Evaluation of efficacy based on complete remission rate (CRR) and overall survival (OS).
- Evaluation of relapse-free survival (RFS), defined as the time from achievement of a CR/CRi after randomization to time of recurrence of the disease or death from any cause, whatever occurs first. Patients without the event are censored on the last date of follow-up.
- Assessment of patient reported outcomes (PRO, including quality of life (QoL)) after induction, consolidation and maintenance therapy and after at least two years
- Evaluation of safety based on duration of neutropenia and leukopenia, incidence of infection, duration of initial hospitalization.
- Cost-effectiveness analysis of the four different treatment schedules from health care payer´s perspective.
- Budget impact analysis of introducing effective treatment schedule(s) in everyday clinical practice.
- Mapping the EORTC QLQ-C30 cancer specific instrument to the SF-36 generic instrument for older patients with newly diagnosed AML in Germany.

Exploratory Objectives encompass the determination of diagnostic, prognostic and predictive markers from biological samples including their potential association with the study treatment.

Trial Design

The study is a multicenter, randomized phase III trial with MRD after induction therapy and event-free survival as primary endpoints. The two research questions are addressed in a 2 by 2 factorial design. Patients are 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 glasdegib as single agent 6 months maintenance therapy (with optional switch from glasdegib to SOC^{PhC}) in a 1:1:1:1 ratio. Patients that were before randomized to placebo during consolidation therapy are as well offered to receive SOC^{PhC} after unblinding.
Chemotherapy backbone for induction therapy is standard 7+3 with cytarabine 200mg/m² continuously day 1 to day 7, daunorubicin 60mg/m² days 1, 2 and 3 and for consolidation therapy intermediate dose cytarabine (1g/m², bi-daily, days 1,2,3). The trial is designed to gain evidence of anti-leukemic activity of gemtuzumab ozogamicin and glasdegib in adult patients with newly diagnosed acute myeloid leukemia.

Investigational Medicinal Product(s)

- Gemtuzumab ozogamicin infusion (Mylotarg®, commercially available drug is used)
- Glasdegib 100 mg tablets and 25 mg tablets (Daurismo®, clinical study supplies are used)

Sample Size

Addressing two primary endpoints, MRD-negativity after induction therapy and EFS, 252 evaluable patients are needed to reject each of the two null hypotheses at a two-sided significance level of 2.5% with a power of at least 85%.

Statistical Analysis

The endpoints MRD-negativity after induction therapy and event-free survival are analyzed using a generalized linear mixed model for MRD-negativity and a Cox regression frailty model for EFS, both adjusting for the fixed factors treatment, age, ECOG PS, and the random factor center, respectively.

Trial Duration and Dates

Total trial duration:	5 years
Duration of the clinical phase:	4 years
First Patient First Visit (FPFV):	Q3/Q4 2020
Last Patient First Visit (LPFV):	Q3/Q4 2022
Last Patient Last Visit (LPLV):	Q3/Q4 2024
Trial Report Completed:	Q3/Q4 2025

Trial Schedule

PHASE	BL	IT[1]	IT[1]	IT[1]	IT[1]	CT	CT	CT	CT	MT	MT	EOT	SA	FU	EOS
DAY (OF CYCLE)	-14-0	1	4,7	15-EOC	EOC[2]	1	2-3	4-EOC	EOC[3]	1-27	28/EOC				
Clinical assessments															
Signs/symptoms	X				X				X		X[3M]	X[O]	X[M]	X[3M,Y]	X
Vital signs	X[Height]	X	X	X[W]	X	X[O]		X[W]	X		X	X[O]	X[M]	X[3M,Y]	X
Physical examination	X	X[O]	X	X[W]	X	X[O]		X[W]	X		X	X[O]	X[M]	X[3M,Y]	X
ECG	X	X[O]				X[O]			X		X	X[O]			X
Extramedullary involvement	X				X				X		X[3M]	X[O,]		X[3M,Y,]	X
ECOG PS	X	X[O]	X	X[W]	X	X[O]			X		X	X[O]	X[M]	X[3M,Y]	X
Laboratory assessments															
Hematology	X	X[SL]	X[SL]	X[SL,W]	X	X[O,SL]		X[SL,W]	X		X	X[O]	X[M]	X[3M,Y]	X
Basic blood chemistry	X	X[SL]	X[SL]	X[SL,W]	X	X[O,SL]		X[SL,W]	X		X	X[O]	X[M]	X[3M,Y]	X
Extended blood chemistry & coagulation	X	X[SL]	X[SL]	X[SL,W]	X	X[O,SL]		X[SL,W]	X		X	X[O]	X[M]		
Local disease assessment	X				X				X		X[3M]	X[O]		X[3M,Y]	X
Central laboratory assessments															
Sample collection (BM, PB)	X			X[15optl]	X				X		X[3M]	X[O]		X[3M,Y]	X
MRD & Disease status	X				X				X		X[3M]	X[O]		X[3M,Y]	X
PROs & Health economics															
Patient Reported Outcomes &SF-36	X[BI]				X				X		X[3M]	X[BI,O]		X[3M,Y]	X
Resource utilization questionnaire					X				X		X[3M]	X[O]			
Treatment															
GO-147 (experimental arm)		X	X												
GO-1 (control arm)		X													
SOC: Chemotherapy		X[1-7]	X[1-7]			X[C]	X[C]								
Glasdegib/ Placebo/ SOC[PhC] during MT						X	X	X[D28]		X	X				
Unblinding									X[2C]						
Drug Compliance									X		X	X[O]			
Safety															
Concomitant medications & treatment	X	X[1-7]	X[1-7]	X[W]	X	X	X	X[W]	X		X	X			
AE assessment		X[1-7]	X[1-7]	X[W]	X	X	X	X[W]	X		X	X	X[M]		
Pregnancy test (WOCBP only)	X	X[O]				X			X[2C]		X	X[O]	X[M]		
Screening and Baseline															
Informed consent	X														
Demographics	X														
Medical/oncologic history	X														
Genetic assessment (central lab)	X														
Cytogenetics	X														
ECHO	X														
Abdominal ultrasound	X														
Urinalysis	X														
Virus diagnostics	X														
Enrollment & Randomization	X														

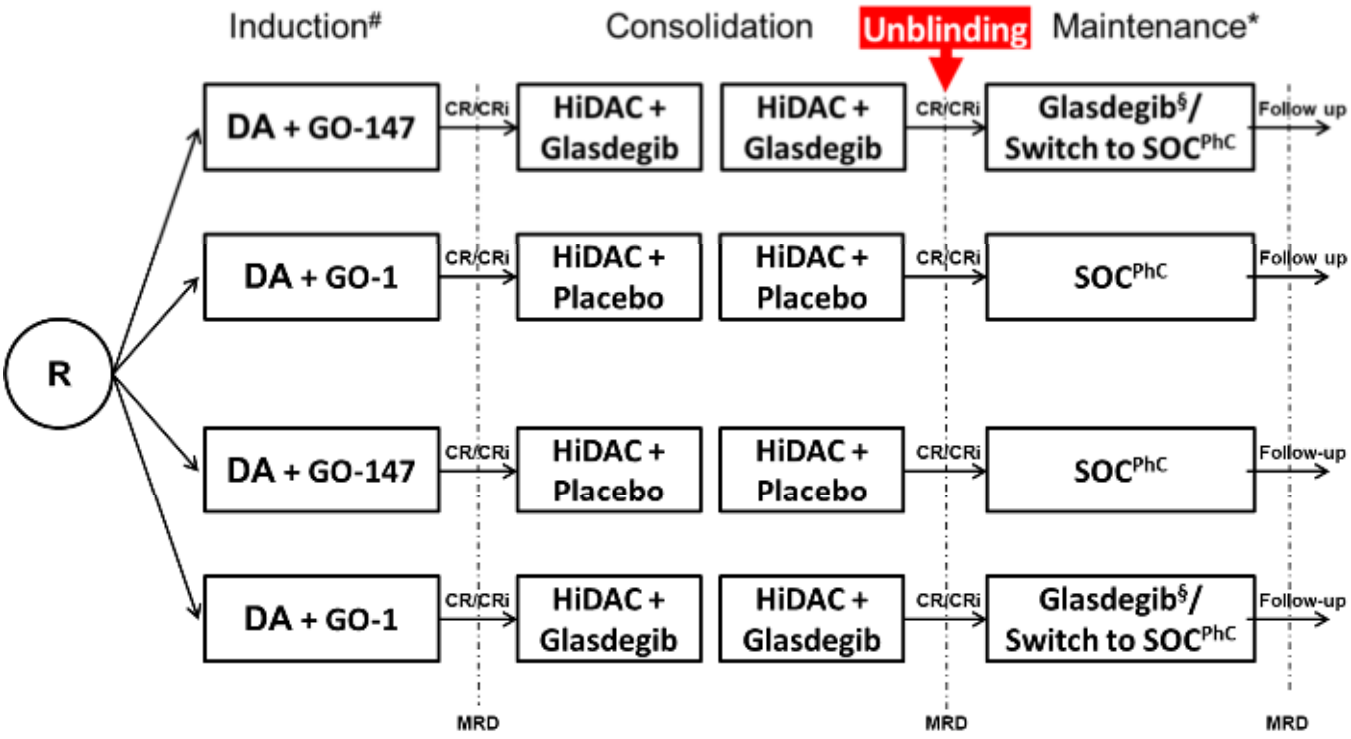
Abbreviations used in the table:

1-7 **Days 1 to 7** (7 days Cytarabine, 3 days Daunorubicine)
2C Only **2nd cycle C**T
3M To be **done 3-monthly**
15optl Optional at **day 15** (- 1 or up to + 3) of IT
BI SF-36 plus background information
BL **Baseline** (within 14 days)
C **Cytarabine** only
CT **Consolidation therapy** (2 treatment cycles and subsequent treatment-free recovery period if needed).
D28 Stop at cycle **day 28**
EOC **End of cycle**
EOS **End of Study** (for all patients: 2 years after LPFV)
EOT **End of treatment** (within 7 days after last intake of glasdegib or at end of CT if going into MT without glasdegib)
FU Observational **follow-up** (3-monthly starting from Last Visit MT until EOS)
Height At baseline incl. height in cm
IT[1] **Induction therapy** (1 treatment cycle at 7 days and subsequent treatment-free recovery period)
M To be done **monthly**
MT **Maintenance therapy** (6 cycles)
O To be **omitted** if done within preceding 48 hours
PhC according to Physicians Choice
SA **Safety Follow-up** (8 weeks after EOT)
SL Safety lab, values not captured in eCRF
SOC **Standard of care**
W To be done in **weekly** intervals (preferably same day per week)
Y After 2 **years** from study day 1, on- site visits are no longer mandatory and may be replaced by contacting the treating physician or mailing the questionnaire. In this case, no more samples are collected.

Further descriptions of the study phases, number of visits and exact days are given in appendix 19.4

[1] conditional salvage therapy cycle not considered, [2] includes treatment-free recovery period of 3-5 weeks, [3] includes treatment-free recovery period of up to 2 weeks if needed.

Flow Chart



Abbreviations:

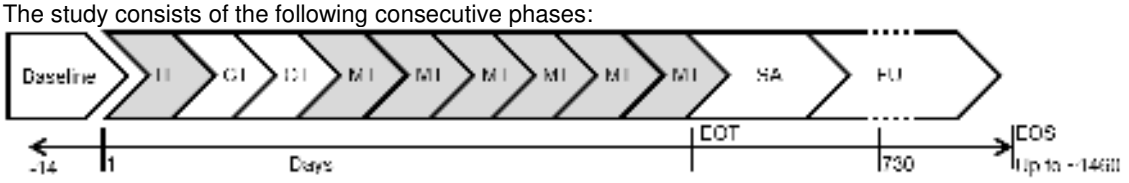
DA, daunorubicin; low-dose cytarabine;
GO, gemtuzumab ozogamicin;
HiDAC, high-dose cytarabine (1g/m²);
SOC^{PhC} Standard of Care according to Physician's Choice
(optional, not stipulated within the scope of study treatment)
MRD, measurable residual disease;
CR, complete remission;
CRi, CR with incomplete hematological recovery
#In case of day 15 bone marrow blast count >10% or no CR/CRi after the induction cycle one cycle of HAM (high-dose cytarabine and mitoxantrone) is allowed
*Maintenance is intended in all patients in CR/CRi irrespective of completion of consolidation therapy.
§Switch to SOC^{PhC} at any timepoint during maintenance feasible

Study Narrative

Overall duration

The study runs until the last patient being alive has been observed for at least 2 years. Assuming 2 years recruitment, the follow-up of the first patient lasts up to 4 years.

The study consists of the following consecutive phases:



BL: Baseline

Up to 14 days prior to inclusion (1st visit). Baseline examnations can be done up to day 1 of induction therapy.

IT: Induction therapy

1 induction cycle with a treatment (SOC chemotherapy plus GO-147/ GO-1) period of 7 days (4 visits) and a subsequent recovery period with no treatment for 3-5 weeks (28-42 days in total / 7 - 9 visits in total, without salvage therapy). Hospitalization is required.

1 conditional salvage therapy cycle (IT-SC) within IT:
In case of **a)** day 15 bone marrow (BM) blast count >10% or **b)** failure to achive CR/CRi after or at day 28 of the induction cycle, one cycle of conditional salvage therapy (IT-SC) with high-dose cytarabine and mitoxantrone (HAM) is allowed (but not mandatory) within the protocol.
In case of **a)** IT-SC starts the earlies at day 21 of IT. In case of **b)** IT-SC starts at day 28 or later.

HAM treatment extends over three consecutive days, followed by weekly disease status evaluation during a recovery period ending between 4 weeks (day 28) and 6 weeks (day 42) after the start of HAM treatment. Dosing and further details, see Section 6.3.

In case of IT-SC, the EOC visit of the induction cycle may be replaced by the end of cycle visit of IT-SC and the EOT visit of the induction cycle is not necessarily to be completed in the eCRF (e.g. in case of **a)**).

Schedule conditional salvage therapy cycle

PHASE	IT	IT-SC	IT-SC	IT-SC	IT-SC	IT-SC
DAY (OF CYCLE)		1	2	3	8-EOC	EOC
Clinical assessments						
Signs/symptoms						X
Vital signs		X	X	X	X^{W}	X
Physical examination		X^{O}			X^{W}	X
ECG		X^{O}				
Extramedullary involvement						X
ECOG PS		X^{O}			X^{W}	X
Laboratory assessments						
Hematology		X	X^{SL}	X^{SL}	$X^{SL,W}$	X
Basic blood chemistry		X			$X^{SL,W}$	X
Extended blood chemistry & coagulation					$X^{SL,W}$	X
Local disease assessment						X
Central Laboratory assessments						
Sample collection (BM, PB)						X
MRD & Disease status						X
PROS & Health economics						
Patient Reported Outcomes						X
Resource utilization questionnaire						X
Treatment						
Cytarabine (BID)		X	X	X		
Mitoxantrone			X	X		
Safety						
Concomitant medications		X	X	X	X^{W}	X
AE assessment		X	X	X	X^{W}	X
Pregnancy test (WOCBP only)		X^{O}				

BID = bi-daily. EOC = End of cycle, IT = Induction Therapy, SC = Salvage Cycle,
SL = Safety lab only, values not captured in eCRF, O = to be omitted if done within preceding 48 hours, W=weekly preferably same day per week

CT: Consolidation Therapy	2 cycles with two treatment periods of 28 days each consisting of 3 days SOC chemotherapy and 28 days glasdegib/placebo, and each with a subsequent treatment-free recovery period of up to 2 weeks if needed (2x 28-42 days = 56-84 days in total). 7-10 visits per cycle. Hospitalization is required.
MT: Maintenance Therapy	Prior to the start of MT all patients are unblinded and patients randomized to the glasdegib arm are offered 6 cycles á 28 days glasdegib, but are also allowed switching to SOC as per Physician's Choice (SOC^{PhC}) at any time during MT. Patients randomized to the placebo arm are offered to receive SOC^{PhC}. MT wil take up to 168 days in total and cover 6-7 visits.
EOT: End of Treatment	Patients failing to obtain CR/CRi after induction therapy (including potential salvage therapy) or relapsing from CR/CRi during consolidation/maintenance therapy are withdrawn from study treatment and followed within the regular follow-up. For patients with persisiting CR/CRi at the end of CT and receiving glasdegib the EoT visit is within 7 days after or on the last day of of glasdegib intake. For patients not receiving maintenance therapy with glasdegib the EoT visit is a the end of consolidation therapy.
SA: Safety	8 weeks safety follow up (56 days in total 2 FU visits) after EOT.
FU: Observational Follow-up	For event-free survival and overall survival, starting after EOT and at least until 2 years counted from day 1.Thereafter, the follow-up may be performed by contacting the treating physician or mailing the questionnaire instead of in-house visits (for maximum 4 years). In this case, no further samples are taken (at least 422 days, at most 1110 days in total, 5-13 FU visits).
EOS: End of Study	The study ends for all patients when the last patient being included and alive has been followed for at least 730 days (2 years) counting from this patient's day 1, which is in the present study equivalent to LPLV.
Allo-HCT	Allogeneic hematopoietic stem cell transplantation (Allo-HCT) is allowed at any time after the end of induction therapy and maintenance therapy may be started thereafter, the earliest at day 30 and the latest at day 100 after transplantation according to initial randomization. From the time of Allo-HCT until resumption of the next therapy cycle no AEs are recorded.

Study Procedures

Clinical assessments	
Signs/symptoms	Standardized assessment of all organ systems.
Vital signs	Weight (in kg), temperature (in degree Celsius) and blood pressure/pulse, height (in cm) only at baseline. In case of death: date and cause if available.
Physical examination	Inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination.
ECG	One 12-lead electrocardiogram.
Extramedullary involvement	Assessment of extramedullary disease status (yes/no) at baseline. In case of extramedullary involvement the extramedullary status has to be re-evaluated at the time of bone marrow evaluation according to European Leukemia Net (ELN) recommendations (see appendix 19.2). Baseline tumor imaging is accepted within 4 weeks prior to the start of treatment.
ECOG PS	See appendix 19.1.
Local laboratory assessments	
General timing	Samples for hematology, blood chemistry and coagulation are to be taken at all time points as shown by the Trial Schedule (page 13). Only values at time points of MRD assessments, during Safety Follow-up (SA) and at day 1 of Salvage Therapy (if applicable) are captured in the eCRF. Laboratory values at additional time points are collected for safety reasons (regarding documentation see below "safety laboratory").
Hematology	Red Blood Cells (RBC), White Blood Cells (WBC), hemoglobin level, hematocrit, mean corpuscular volume (MCV), platelet count, blood differential in case of leukocytes ≥1 G/L. Remission status within SOC.
Basic blood chemistry	Sodium, potassium, calcium, creatinine, uric acid

Extended blood chemistry and coagulation	Lactate dehydrogenase (LDH), Alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (AP), gamma glutamyl transferase (GGT), bilirubin total, direct bilirubin in case of elevated total bilirubin, Partial Thromboplastine Time (PTT) + International Normalized Ratio (INR).
Safety laboratory	Laboratory values that are collected for safety reasons only are not captured as such in the eCRF. If significantly deviating from normal range, and/or assessed by the investigator as clinically relevant, results of safety lab investigations are to be documented as adverse events (AEs) on the appropriate forms of the eCRF.
Local Disease assessment	Disease Status assessments to be done according to 2017 European Leukemia Net (ELN) criteria (see appendix 19.2). The local disease assessment determines all immediate treatment decisions but may be outvoted by central disease assessment in case of contradictory results. Upon treatment failure or relapse, treatment is discontinued and the respective patient is followed within the regular Follow-up.
Central laboratory assessments	
Sample collection (BM, PB)	Collection of bone marrow (BM) aspirates (EDTA, Heparin), unstained BM slides, peripheral blood (PB) (Heparin) and PB smears, see Section 7.3.2 for more details. Sample collection for local and central assessment can be taken 14 days before study entry and up to day one of IT, provided the informed consent form (ICF) has been signed.
MRD & Disease status	Central Assessment of MRD by flow cytometry according to ELN guidelines. Central Disease Status assessments to be done according to 2017 ELN criteria (see appendix 19.2). Upon treatment failure or relapse, treatment is discontinued and the respective patient is followed within the regular Follow-up. In case of contradictory results, the central disease status outvotes the local disease assessment for final analysis.
Patient Reported Outcomes (PROS) and health economics	
Patient Reported Outcomes (PRO)	PROs are assessed by questionnaires of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Item Library (core questionnaire QLQ-C30, fatigue module QLQ-FA12, and selected symptom items), as well as the Pittsburgh Sleep Quality Index (PSQI), the Patient Health Questionnaire for anxiety and Depression (PHQ-4), and the Functional Assessment of Cancer Therapy - cognitive function scale (FACT-cog). In addition, patient-reported information on personal traits and experiences are collected at baseline. Moreover the Short Form Health 36 questionnaire (SF-36) is used for a mapping study (between generic SF-36 and cancer specific EORTC QLQ-C30) within the scope of health economic analyses (see below). The paper based questionnaires are mailed or handed over to the patients at the study site on different time points of the study, for further details see trial schedule at page 13.
Health care resource utilization	Health care resource utilization is assessed by self-administered resource utilization questionnaire. In addition SF-36 questionnaires are administered within the scope of health economic analyses (see above, PROs), further details see Section 7.4.6 and Section 7.5
Treatment	
GO-147 (experimental arm)	Gemtuzumab ozogamicin given on days 1, 4 & 7 during IT cycle, dosing and further details see Section 6.3.
GO-1 (control arm)	Gemtuzumab ozogamicin given on day 1 during IT cycle, dosing and further details, see Section 6.3.
SOC: Chemotherapy	During IT cycle 7 days Cytarabine and 3 days Daunorubicin (with respect to SOC of conditional salvage therapy cycle during IT see above), during CT 3 days Cytarabine, dosing and further details, see Section 6.3.
Glasdegib / Placebo	Glasdegib for 28 days during each cycle of CT and MT (if not switched to SOC^{PhC}), placebo for 28 days during each cycle of CT, dosing and further details, see Section 6.3.
Unblinding	All patients are unblinded post consolidation therapy (prior to starting maintenance therapy)
Drug Compliance	Dates of drug intake and all missed doses must be recorded. Bottles (empty or containing unused tables) and dosing diaries are to be returned.
Safety	
Concomitant medications/ treatment	Concomitant medications and treatment including duration of initial hospitalization have to be reported in the respective electronic case report form (eCRF), including supportive care drugs and drugs used for treating adverse events (AEs) or chronic diseases.

Safety laboratory	Laboratory values that are collected for safety reasons only are not captured as such in the eCRF. If significantly deviating from normal range, and/or assessed by the investigator as clinically relevant, results of safety lab investigations are to be documented as adverse events (AEs) on the appropriate forms of the eCRF.
AE assessment	Events have to be documented and recorded continuously. Patients must be followed for AEs up to 28 days after last study drug administration or until all drug-related toxicities have been resolved, whichever is later, or until the investigator assesses AEs as “chronic” or “stable”. However, if the patient commences alternative anti-cancer therapy <28 days after the last dose of study drug administration, the AE reporting period ends at the time the new treatment is started. Each AE must be reported once per cycle, indicating the worst Common Toxicity Criterion AE grade (CTCAE) (Version 5.0). If an event stops and later restarts within the same cycle, all occurrences must be reported. A specific procedure for definition and reporting of serious adverse events (SAEs) is described in Section 9.1.2.
Screening and Baseline	
General timing	Screening measures can be accomplished over one or multiple visits over a 2-week period (14 days). Baseline examinations (if applicable results are are not anyhow existing from standard of care procedures) can be done up to 14 days prior to study entry, given the informed consent is signed. If needed, Baseline examinations may be performed on IT day 1, given all inclusion criteria are met and the patient singed the informed consent. Baseline day 0 and IT day 1 may be on the same day. Patients may be re-screened if they did not pass all eligibility criteria.
Informed consent	Every patient must date and sign the informed consent to participate in this trial. Protocol specific tests or procedures not considered standard of care can only be done after the patient has agreed on trial participation and signed the Informed Consent document. However, bone marrow examinations done as part of the clinical routine to diagnose AML can serve as baseline examinations if done up to 14 days before signing the informed consent (but no longer than 14 days prior to initiation of treatment), if the patient explicitly agrees to this. The Informed Consent document may be signed maximally up to 14 days prior to initiation of treatment. In case of re-screening patients must re-consent but keep their screening number. If a patient ID has already been assigned, this is kept as well.
Demographics	Sex, year of birth, ethnicity
Medical/oncologic history	Date of first diagnosis detailed information on diagnosis of AML, cancer history including history of the closer family circle (parents, brothers/sisters, children) , additional medical history on concomitant diseases, prior exposure to toxic agents, prior malignancy including therapy, information on smoking.
Genetic Assessment (central lab)	Molecular profiling is performed at the central laboratory using the “TruSight Myeloid Sequencing Panel” from Illumina and RT-PCR for fusion genes including *BCR-ABL1, PML-RARA* (exclusion criteria)*, RUNX1-RUNX1T1, CBFB-MYH11, MLLT3-KMT2A, DEK-NUP214.*
Cytogenetics	Cytogenetics performed by R-banding or G-banding analysis at local lab.
ECHO	Echocardiography at baseline and thereafter at investigator’s discretion
Abdominal ultrasound	Abdominal ultrasound at baseline and thereafter at investigator’s discretion
Urinalysis	pH, glucose, proteins (qualitative, dipstick accepted): at baseline and at investigator’s discretion during treatment. (local lab)
Virus diagnostics	HBV surface antigen (HBsAg), Hepatitis B surface antibody (Anti-HBs), Hepatitis B core antibody (anti-HBc), HCV antibody Immunoglobuline G (Anti-HCV IgG), in case of positive anti-HCV IgG HCV load, Anti-HAV IgM, HIV test at baseline and thereafter at investigator’s discretion. (local lab)
Pregnancy test (WOCBP only)	In WOCBP, a pregnancy test must be performed at baseline (local lab, sensitivity of at least 25 mIU/mL) and at the onset of each cycle with Investigational Medicinal Product (IMP)/placebo administration. Pregnancy test may be performed 48h earlier than scheduled. In addition, WOCBP and male patients must be counseled to avoid getting pregnant or to father a child within three months after the last application of therapy.
Enrollment & Randomization	The investigator is requested to sign the request for enrollment form in the eCRF. This signature guarantees that eligibility criteria are met and a unique patient identifier (PAT-ID) is assigned. Randomization is carried out by the responsible investigator online. The random-number (Rand-No) is assigned.

Abbreviations

AE	Adverse Event
ALT	Alanine Amino Transferase, also known as SGPT
Allo-HCT	Allogeneic Hematopoietic Stem Cell Transplantation
AMG	German Drug Law (Deutsches Arzneimittelgesetz)
AML	Acute myeloid leukemia
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
Anti-HCV IgG	HCV antibody Immunoglobuline G
AST	Aspartate Aminotrans-ferase, also known as SGOT
AP	Alkaline Phosphatase
BM	Bone Marrow
BMed	Background Medication
CBC	Complete Blood Cell Count
CHF	Chronic Heart Failure
CI	Coordinating Investigator (LKP)
CNS	Central Nervous System
CR	Complete Remission
CRi	Complete Remission with incomplete Hematological Recovery
CRR	Complete Remission Rate
(e)CRF	(electronic) Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CT scan	Computed Tomography Scan
CYP3A4/5	Cytochrome P450 3A4/5
DBL	Data Base Lock
DFG	Deutsche Forschungsgemeinschaft
Dhh	Desert Hh
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	Event-free Survival
ELN	European Leukemia Net
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
EOT	End of Treatment
FACT-cog	Functional Assessment of Cancer Therapy - cognitive function scale
FDA	U.S. Food and Drug Administration
FPFV	First Patient First Visit
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GCP-V	GCP Regulation (GCP-Verordnung)
GGT	Gamma Glutamyl Transferase
GliA	Gli Activator
GliR	Gli Repressor
GO	Gemtuzumab ozogamicin
HAM	High-dose Cytarabine and Mitoxantrone
HDPE	high-density polyethylene
Hh	Hedgehog
HiDAC	High-dose Cytarabine
HBV	Hepatitis B Virus
HBsAg	HBV surface antigen
HCV	Hepatitis C Virus
HHIP	Human Hh-interacting Protein
HIV	Human Immunodeficiency Virus
HMA	hypomethylating agent
IB	Investigator´s Brochure
ICD	International Classification of Diseases
ICH	International Conference on Harmonization of Tech-nical Requirements for Registration of Pharma-ceuticals for Human Use
ICTRP	International Clinical Trials Registry Platform
Ihh	Indian Hh
IIR	Investigator Initiated Research Study

IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
IT-SC	Induction Therapy – Salvage Cycle
ITT	Intention To Treat
IUS	Intrauterine Hormone Releasing System
IUD	Intrauterine Device
KKS	Coordination Center for Clinical Trials (Koordinierungszentrum für Klinische Studien)
LDH	Lactatdehydrogenase
LKP	Coordinating Investigator according to AMG (Leiter der Klinischen Prüfung)
LLN	Lower Limit of Normal
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
LSC	Leukemic Stem Cell
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	modified ITT
MR	Minor Responses
MRD	Measurable Residual Disease
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association classification
OS	Overall Survival
PTCH	Patched
PAT-ID	Patient Identifier
PB	Peripheral Blood
PD	Progressive Disease
PHQ-4	Patient Health Questionnaire for anxiety and Depression
PP	Per Protocol
p.o.	per os/ per oral/ orally
PRO	Patient Reported Outcome
PSQI	Pittsburgh Sleep Quality Index
PT	Prothrombin Time
PTT	Partial Thromboplastine Time
QALYs	Quality Adjusted Life Years
QD	Once a Day
QoL	Quality of Life
QTc(F)	Corrected QT interval (using Fridericia Formula)
Rand-No	Randomization number
RBC	Red Blood Cells
RDE	Remote Data Entry
RFS	Relapse-free Survival
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAL	Study Alliance Leukemia
SC	Steering Committee
SD	Stable Disease
SDV	Source Data Verification
SF-36	Short Form Health 36 questionnaire
Shh	Sonic Hh
SGPT	Serum Glutamic-Pyruvat Transaminase, also known as ALT
SGOT	Serum Glutamic-Oxal-oacetic Transaminase, also known as AST
SMO	Smoothened
SMOi	Smoothened Inhibitor
SmPC (SPC)	Summary of Product Characteristics
SOC	Standard of Care
SOC^{PhC}	Standard of Care according to Physician's Choice
SOS	Sinusoidal Obstruction Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
ULN	Upper Limit of Normal
VOD	Veno-occlusive Disease
WBC	White Blood Cells
WOCBP	Women of Childbearing Potential
WHO	World Health Organization

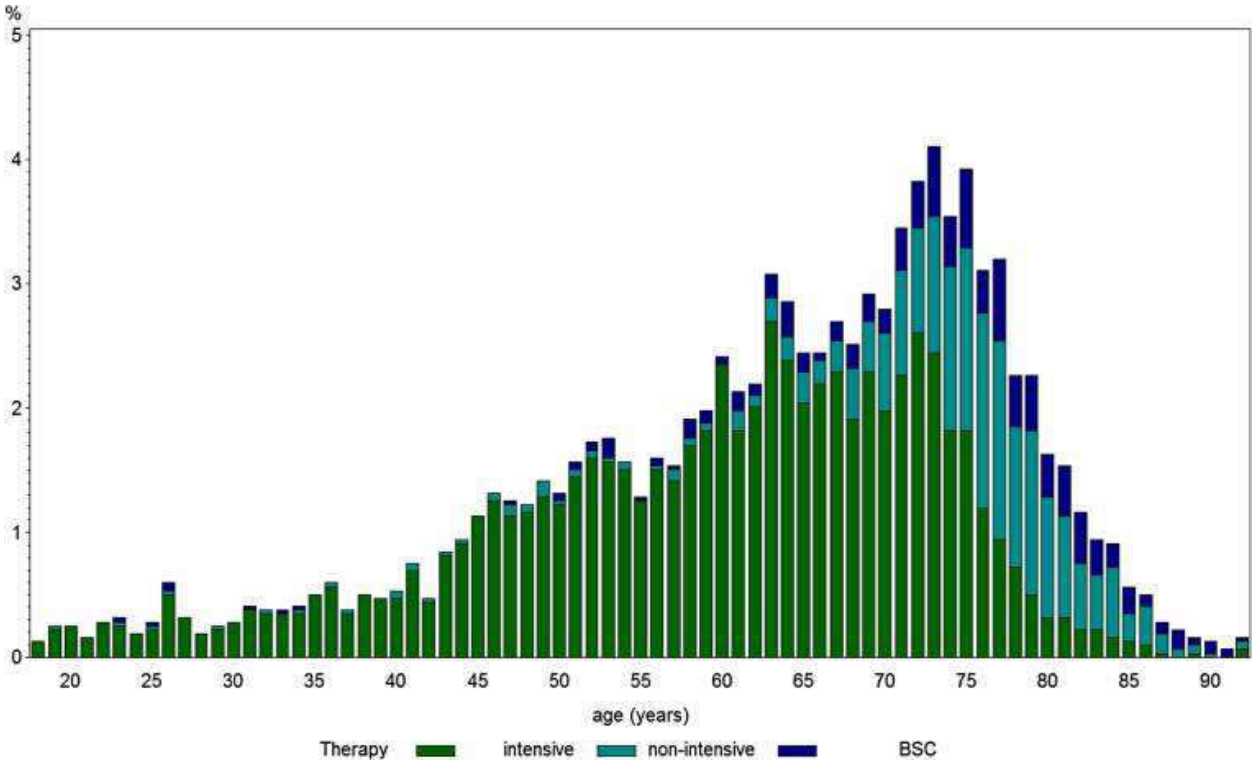
1 Introduction

1.1 Scientific Background

1.1.1 AML

Acute myeloid leukemia (AML) is predominantly a disease of older patients for which prognosis is still poor [1][2]. Intensive induction chemotherapy, usually consisting of an anthracycline and cytarabine. Once a first complete remission (CR) is achieved, approximately half of the younger (≤60 years) patients and about 80-90% of the older patients still relapse despite intensive consolidation therapy, and the majority of relapsed patients succumb to their disease [2][4][55]. Beyond patient-associated factors such as increasing age, comorbidities and poor performance status, disease-related factors such as the genetic profile of the diseased predicts resistance to current standard therapy [3]. In line, the proportion of patients with a high risk disease profile according to ELN-2010 risk classification [4] increase with an increasing age to roughly one quarter of patients 70 years or older [5]. Combination of an anthracycline with cytarabine ('3+7') remains the standard of care of intensive induction therapy in patients considered medically fit [1][2] and the proportion of patients receiving intensive chemotherapy even in older patients is high with 80% to 90% in 60 to 70-year-old patients and 50% to 75% in patients aged between 70 and 75 years (Figure 1) [5]. In patients who achieve a complete remission (CR) after induction chemotherapy, postremission therapy is required to prevent relapse. However, despite intensive consolidation therapy age-standardised relative 5-year survival for adult patients diagnosed between the years 2000 and 2007 was as low as 17% (16.6–17.7), mainly attributable to the minimal progress attained in AML patients older than 65 years [55].

Figure 1: Frequency of treatment strategy (intensive, non-intensive and best supportive care (BSC)) according to age



Source: [5]. Abbreviation: BSC, best supportive care

AML is a disease with large differences in prognosis. Age and genetic abnormalities constitute the strongest prognostic factors for survival [7][8]. This is clearly reflected in the current WHO classification of myeloid neoplasms and acute leukemia (see appendix 19.3) [9]. The ELN risk classification has recently been updated (in 2017) to include new clinical, prognostic,

morphologic, immunophenotypic, and genetic data that emerged over the last 6 years. The current risk classification system defines three risk categories: favorable, intermediate and adverse (see appendix 19.2) [4].

1.1.2 Gemtuzumab Ozogamicin in AML

Gemtuzumab ozogamicin (GO) is a humanized immunoglobulin G4 antibody (hP67.6) directed against CD33 and conjugated via a hydrolysable linker to the DNA toxin calicheamicin. GO/CD33 complexes are internalized into lysosomes, releasing calicheamicin and promoting single and double-strand breaks and cellular death. GO initially received accelerated approval by the U.S. Food and Drug Administration (FDA) in 2000 for the treatment of CD33+ AML aged ≥60 years in first relapse [10], with the requirement that the company undertakes a confirmatory postmarketing study [11]. A phase 3 study (S0106) was conducted by SWOG Cancer Research Network in untreated de novo AML, comparing daunorubicin/cytarabine (DA), using a dose of 45 mg/m² daunorubicin, plus GO 6 mg/m² on day 4 versus DA alone using a dose of 60 mg/m² daunorubicin. The GO arm had higher induction mortality (5.5% vs 1.4%), without improving CR or relapse-free survival [11]. Based on these negative results GO was withdrawn from the market in 2010. Meanwhile, 4 additional investigator initiated randomized studies have been completed in Europe: GOELAMS AML2006IR [12], MRC AML15 [13] and ALFA-0701 [14], NCRI AML16 [15]. ALFA-0701 randomized 278 patients with untreated de novo AML aged 50 to 70 years to DA (60 mg/m² daunorubicin) alone or in combination with a fractionated GO induction schedule (3 mg/m² on days 1, 4, and 7) [14]. Although CR with or without platelet recovery and early deaths were similar, patients in the GO arm had significantly improved median event-free survival (19.6 vs 11.9 months; Pp=.00018) and OS (34 vs 19.2 months; p=.046). A subgroup analysis revealed that the clinical benefit is mainly restricted to patients with favorable and intermediate-risk karyotype. However, an updated analysis after extensive data review excluding 9 patients revealed that OS was not significantly improved (p=.16) [16]. A meta-analysis of 3,325 patients from 5 randomized studies mentioned above in untreated AML (aged 18-84) concluded that GO improved OS in patients when combined with standard induction chemotherapy [17]. Rates of sinusoidal obstruction syndrome (SOS) and 30- and 60-day mortality were lower with 3 mg/m² vs 6 mg/m² GO [18]. In contrast to all other studies reported in the meta-analysis Castaigne et al. reported on fractionated gemtuzumab ozogamicin (GO) in a dosage of 3 mg/m² on days 1, 4 and 7 (GO-147) as adjunct to intensive induction chemotherapy [14]. Interestingly, the addition of GO to induction therapy did not lead to a significantly improved CR rate but a significantly higher rate of patients being negative for measurable residual disease (MRD-negative, 7% versus 39% in the standard and experimental arm, respectively) [19]. In addition fractionated GO-147 compared to one day GO-1 showed in the large meta-analysis the highest beneficial impact on all survival endpoints. However, this comparison was not based on an upfront randomization and thus it is still unclear whether fractionated GO-147 is superior to GO-1 (3mg/m²). A major concern for patients receiving GO is the risk of sinusoidal obstruction syndrome (SOS), especially among patients who received allogeneic hematopoietic stem cell transplantation (Allo-HCT) within 3 months [20]. Revised dosing schedules significantly lowered rates of SOS towards expected levels in patients being GO-naive [14][21][22].

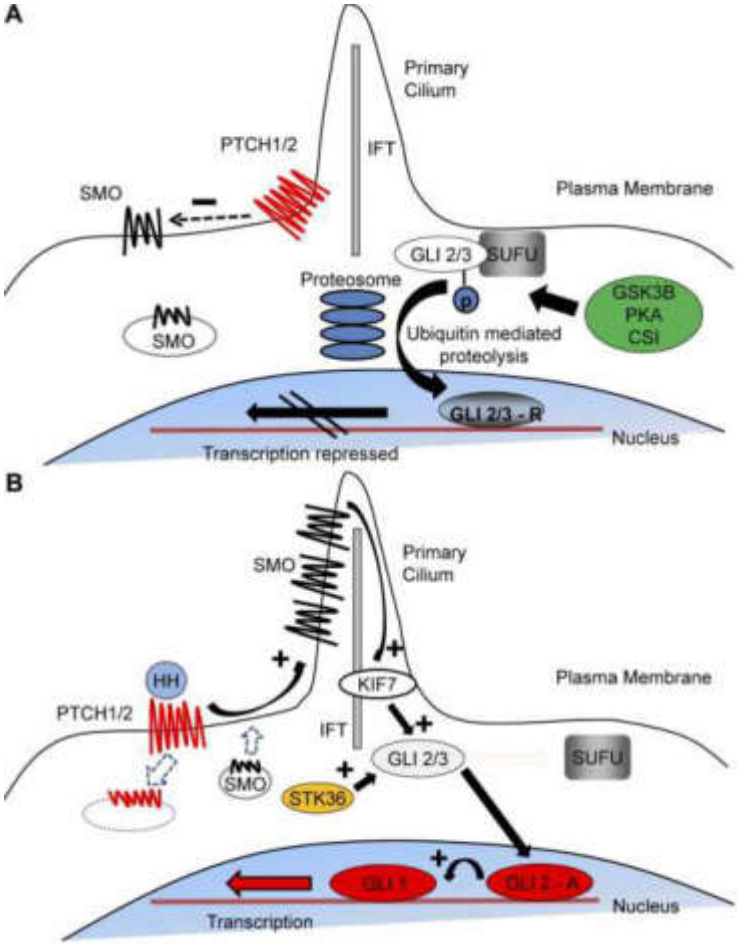
1.1.3 Glasdegib and the Hedgehog (Hh) Pathway Signaling

A milestone in perceiving cancer as a disorder of differentiation and development was the identification of cancer stem cells that self-renew, initiate, and re-initiate tumor development and give rise to the bulk of the tumor. The persistence of such tumor-initiating cells may contribute to tumor resistance and impact overall survival. Standard chemotherapy, radiotherapy and targeted therapies reduce tumor bulk, but are less effective at targeting tumor-initiating cells. The key challenge has been to identify the molecular mechanisms maintaining and sustaining tumor-initiating cell activity, self-renewal and survival. Hh signaling is critical in terminal cell differentiation during embryogenesis, and may play a key role in human malignancies when aberrantly activated. Following birth, the Hh pathway is repressed in most cells, but activated during tissue repair and in self-renewing populations. Hh signaling is initiated when the Hh ligands: Indian Hh (Ihh), Sonic Hh (Shh), and/or Desert Hh (Dhh) bind to the transmembrane protein Patched (PTCH) and inactivate its function, and thus inhibiting Smoothened (SMO) signal

transduction. Following deactivation of PTCH in response to the binding of Hh ligands, the seven-transmembrane protein SMO, which is normally held in an inactive state by PTCH, is released and activates a signaling cascade that regulates the Gli family of transcription factors (Figure 2) [23][24]. The Gli family of genes encode proteins that function either as transcriptional repressors (in the absence of Hh), or as transcriptional activators (in the presence of Hh) of genes controlled by the Hh pathway. Several proteins modulate the ratio of Gli activator (GliA) to Gli repressor (GliR) activity and in so doing determine the level of active cellular Hh ligand (Figure 2) [23][24].

Since its initial description, the Hh pathway has received increasing attention as a pleiotropic oncogenic pathway, and its aberrant activity has been implicated in both hematopoietic and solid tumor malignancies through a range of different mechanisms, including a direct cell cycle and anti-angiogenic effect [25][26]. Given that these cell types and mechanisms are unrelated in developmental origin, site, and function, a common dependence of tumor-initiating cells on Hh-Gli signaling for survival and self-renewal, paralleling its roles in normal development and homeostasis, may underlie its involvement in human cancers [27]. An important caveat, is that the Hh signaling pathway is dispensable for adult hematopoietic stem cell function [28].

Figure 2: The mechanism of Hh signal transduction [24]



(A) In the resting state, PTCH 1/2 is expressed on the plasma membrane and acts to repress SMO activity by preventing its expression and localization to the primary cilium. GLI2/3 transcription factors are within a complex, including SUFU, an inhibitor of Hh signaling. This conformation promotes nonspecific phosphorylation of the C terminus by GSK3, CSI, and PKA, resulting in E3 ubiquitin ligase activity and subsequent partial proteasomal proteolysis to the C terminal truncated repressor form. After translocation to the nucleus, the repressive forms of GLI2 (GLI2-R) and particularly GLI3 (GLI-3R) potently inhibit the Hh transcriptional program.

(B) Interaction of Hh ligand with PTCH promotes PTCH internalization and degradation and releases the repression of SMO, causing its accumulation within the primary cilium. Active SMO in the primary cilium stabilizes the full-length forms of GLI2 (GLI2-A) and GLI3 (GLI3-A) and accentuates the effect of other positive regulators of Hh signaling, including serine threonine kinase 36 (STK36) and kinesin family member 7 (KIF7), which may be involved in translocation of GLI into the primary cilium. After translocation to the nucleus, GLI2-A potently activates transcription of downstream Hh targets, including GLI1 and PTCH1, and influences chromatin conformation, apoptosis, cell cycle activity, and differentiation.

The expression of Hh-related genes has been assessed in primary human CD34+ cells, CD34+blastic cells (from MDS and AML patients) and BM stromal cells. Both Ihh and its signal transducer SMO, were expressed in CD34+ AML and MDS-derived cells. Moreover the expression of the intrinsic Hh-signaling inhibitor, human Hh-interacting protein (HHIP) was markedly lower in AML/MDS-derived stromal cells as compared with healthy donor-derived stromal cells. Furthermore, in vitro treatment with azacitidine rescued the HHIP expression via demethylation of HHIP gene and reduced the leukemic cell-supporting activity of AML/MDS-derived stromal cells [29]. These data demonstrate the relevance of Hh signaling in primary

CD34+ blasts derived from AML and MDS and confirm its involvement in shaping the BM microenvironment during the development of myeloid malignancies.

In preclinical AML models, SMO, acting via its effector GLI2, has been implicated in the maintenance of leukemic stem cell (LSC) dormancy and associated resistance to chemotherapy and targeted therapy, while inhibition of SMO via glasdegib can cause LSCs to re-enter the cell cycle [30][31][32]. Recrudescence of LSCs is prevented in preclinical hosts pre-treated with Hh pathway inhibitors, including glasdegib [30]. Consistent with these effects, glasdegib sensitized AML cells to cytosine arabinoside, and abrogated resistance to cytosine arabinoside in AML cells co-cultured with stromal cells [30].

Aberrant activation of the Hh signaling pathway has been implicated in the maintenance of LSC populations in several model systems [30]. Glasdegib is a selective, small-molecule inhibitor of SMO, a membrane protein that regulates the Hedgehog pathway. In vivo treatment of AML cells with glasdegib attenuated the leukemia-initiation potential in a serial transplantation mouse model [30]. Comprehensive gene set enrichment analysis revealed that glasdegib modulates self-renewal signatures and cell cycle progression [31]. These encouraging results have been supported by clinical data. In a phase I study the maximally tolerated dose was defined with 400mg daily and recommended phase II dose was 200mg daily or less [33]. In a randomized phase 2 study for older patients not fit for intensive chemotherapy the addition of glasdegib 100mg daily to low-dose cytarabine resulted in significantly better CR rate and overall survival compared to low-dose cytarabine alone [34]. Inline, encouraging results of a first interim analysis of the open-label, multicenter, phase 1b BRIGHT MDS & AML 1012 (NCT02367456) trial reported a CR of 20.0% (n = 6) after a median follow-up time of 7.8 months in patients unable to receive intensive chemotherapy or age ≥ 75 years with AML and receiving treatment with glasdegib and azacytidine [56].

Glasdegib was approved by the FDA in 2018 and since June 2020, Glasdegib in combination with low-dose cytarabine is approved by the European Medicines Agency (EMA) for the treatment of adult patients with AML ineligible for standard chemotherapy. The role of glasdegib in the consolidation scenario is still unclear and further trials are urgently needed.

1.1.4 Current treatment approaches of AML

With the exception of old and frail patients, most AML patients are eligible for intensive chemotherapy, which is given in curative intent consisting of induction and consolidation therapy [2][4][5]. However, despite intensive therapy, the long-term outcome of AML patients remains poor, with less than 30% of patients achieving long lasting remission and even cure [1][2]. This poor outcome is largely due to refractoriness to induction chemotherapy as well as relapses during and after completion of intensive induction and consolidation therapy. Regarding refractoriness, about 20-30% of AML patients under the age of 60 years and about 50% of older patients fail to attain complete remission (CR) following cytarabine plus anthracycline based standard induction therapy [35][36][37]. Regarding relapses, even patients having achieved complete remission are at a high risk of relapse, particularly within the first two years after completion of chemotherapy [38]. In particular, overall survival in older patients with AML remains poor with less than 10% alive after 5 years. Reasons for this dismal outcome are lower complete remission rates after intensive induction therapy compared to younger patients and a high risk of relapse despite intensive consolidation therapy [1][3][4].

1.2 Trial Rationale/ Benefit- Risk Assessment

In the AMLSG 09-09 phase III study, 588 patients older than 18 years and considered eligible for intensive therapy were randomly up-front assigned to induction therapy with idarubicin, cytarabine, etoposide, and all-trans-retinoic acid either with or without GO. The cumulative incidence of relapse (CIR) in patients achieving a complete remission (CR) or CR with incomplete hematologic recovery (CRi) was significantly reduced in the GO arm as compared with the standard arm (P = .005), whereas no difference in the cumulative incidence of death (*P* = .80) was observed.

In a companion study evaluating NPM1 MRD during the trial, overall, the addition of GO reduced significantly the MRD levels at all time-points compared to the standard arm. This study clearly demonstrated the value of consolidation therapy with high-dose cytarabine, since NPM1 MRD was significantly and sequentially reduced during the 3 consolidation cycles in the standard- as well as in the GO-arm of the study, what strongly supports the concept of intensive post-remission therapy. However, despite achieving NPM1 MRD negativity after consolidation therapy, still one-quarter of the patients relapse within 4 years [57].

In the ALFA-0701 study fractionated gemtuzumab ozogamicin (GO) was given in a dosage of 3 mg/m² on days 1, 4 and 7 (GO-147) as adjunct to intensive induction chemotherapy in the experimental arm [14][16]. In this randomized study the authors showed a significantly improved event-free and relapse-free as well as numerically but not statistically significant overall survival by the addition of GO in older patients (50 to 70 years) with newly diagnosed AML compared to the same treatment without GO. Interestingly, the addition of GO to induction therapy did not lead to a significantly improved CR rate but a significantly higher rate of patients being negative for measurable residual disease (MRD-negativity, 7% versus 39% in the standard and experimental arm, respectively) [19]. In a large meta-analysis including five randomized trials, the addition of GO to intensive chemotherapy reduced the risk of relapse and improved overall survival in younger and older AML patients [17]. Based on these data GO was re-approved by the FDA in September 2017 [39]. Based on the meta-analysis, addition of GO in a dosage of 3mg/m² to intensive induction therapy could safely be administered but uncertainty remained concerning the optimal schedule, fractionated on days 1, 4 and 7 as in the ALFA trial or as in the other 4 studies applied only for one day. Thus, the up-front randomized comparison of GO-147 versus GO-1 as adjunct to intensive induction therapy appears as a logic consequence in terms of efficacy and safety.

Despite intensive consolidation therapy more than 50% of all patients relapse and die of their disease. Therefore, the intensity and duration of consolidation therapy is still a matter of debate [6]. Again, achievement of MRD-negativity after consolidation is associated with a reduced relapse-risk and better survival. This indicates that relapse is triggered by residual leukemia stem cells which are not well targeted by standard intensive chemotherapy. Aberrant activation of the Hedgehog signaling pathway has been implicated in the maintenance of leukemia stem cell populations in several model systems. Glasdegib is a selective, small-molecule inhibitor of SMO, a membrane protein that regulates the Hedgehog pathway. Based on the compelling preclinical data and the results of the phase-I and randomized phase-II studies it appears reasonable and clinically feasible to combine standard intensive consolidation therapy with glasdegib. Therefore, the double blinded randomized comparison of glasdegib versus placebo as adjunct to intensive consolidation therapy followed by a 6 months single agent maintenance therapy appears again as a logic next step in drug development.

1.2.1 Justification for the use of Placebo

In this study glasdegib or placebo is added to standard of care chemotherapy during consolidation therapy to investigate if the addition of glasdegib is beneficial. Patients of the control group are taking placebo in addition to active standard treatment, i.e. they receive the approved and recommended standard regimen. Hence, patients of the control have no disadvantage as compared to patients outside the study. Based on this the use of placebo is justified and necessary to achieve highest scientific validity.

1.2.2 Consideration of SARS-CoV-2 Pandemic

Newly diagnosed myeloid leukemia is a medical/hematological urgency. Without treatment 50% of the patients die within 3 months and survival after one year is below 5%. Therefore, all patients are treated immediately whenever possible. In addition, despite intensive chemotherapy most patients relapse and die of their disease. Therefore there is a high medical need to improve outcome in this patient population. This can only be achieved, if patients are treated within clinical studies and this applies as well during the SARS-CoV-2 pandemic.

1.3 Reference Committees

1.3.1 Data Monitoring Committee (DMC)

A DMC is assembled. The DMC is composed of three independent experts, assessing the progress and safety data. The mission of the DMC is to ensure the ethical conduct of the trial and to protect the safety interests of patients in this trial.

The DMC meets virtually 6-monthly. Based on its review, the DMC provides the sponsor with recommendations regarding trial modification, continuation or termination.

Further details including DMC members are specified in the DMC charter.

The DMC charter is set up in accordance with applicable guidelines (EMEA/CHMP/EWP/5872/03 Corr, ICH Guidelines E3 E6, E9, Directive 2001/20/EC).

2 Trial Objectives

2.1 Primary Objectives

The primary objectives of the present trial are:

- To assess clinical efficacy of sequential or one-dose gemtuzumab ozogamicin as adjunct to induction therapy in adult patients with newly diagnosed AML. Clinical efficacy is determined by 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, with an optional switch to SOC according to Physician's Choice during maintenance (SOC^{PhC}), in older patients with newly diagnosed AML. Clinical efficacy is determined by event-free survival (EFS) defined as the time from randomization to time until one of the following events, whichever occurs first: a) failure to obtain complete remission (CR) or complete remission with incomplete hematological recovery (CRi), b) relapse from CR/CRi for patients with induction success or c) death from any cause. Patients without an applicable event are censored on the last date of follow-up.

2.2 Secondary Objectives

The secondary objectives of the present trial are:

- Evaluation of efficacy based on complete remission rate (CRR) and overall survival (OS).
- Evaluation of relapse-free survival (RFS), defined as the time from achievement of a CR/CRi after randomization to time of recurrence of the disease or death from any cause, whatever occurs first. Patients without the event are censored on the last date of follow-up.
- Assessment of patient reported outcomes (PRO, including quality of life (QoL)) after induction, consolidation and maintenance therapy and after at least two years
- Evaluation of safety based on duration of neutropenia and leukopenia, incidence of infection, duration of initial hospitalization.
- Cost-effectiveness analysis of the four different treatment schedules from health care payer´s perspective.
- Budget impact analysis of introducing effective treatment schedule(s) in everyday clinical practice.
- Mapping the EORTC QLQ-C30 cancer specific instrument to the SF-36 generic instrument for older patients with newly diagnosed AML in Germany.

Primary and secondary endpoints are described Section 10.2.

2.3 Exploratory Objectives

- Determination of diagnostic, prognostic and predictive markers from biological samples including their potential association with the study treatment

3 Trial Design

The study is a multicenter, randomized phase III trial with MRD after induction therapy and event-free survival as primary endpoints. The two research questions are addressed in a 2 by 2 factorial design. Patients are 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 glasdegib as single agent 6 months maintenance therapy (with optional switch from glasdegib to SOC^{PhC}) in a 1:1:1:1 ratio. Patients that were before randomized to placebo during consolidation therapy are as well offered to receive SOC^{PhC} after unblinding.
Chemotherapy backbone for induction therapy is standard 7+3 with cytarabine 200mg/m² (in patients >70 years optionally 100mg/m²) continuously day 1 to day 7, daunorubicin 60mg/m² days 1, 2 and 3 and for consolidation therapy intermediate dose cytarabine (1g/m², bi-daily, days 1,2,3).

The trial is designed to gain evidence of anti-leukemic activity of gemtuzumab ozogamicin and glasdegib in adult patients with newly diagnosed acute myeloid leukemia.

See Section 6.3 for the details on the administration schedule.

4 Trial Duration and Schedule

Trial Duration and planned Dates

Total trial duration:	5 years
Duration of the clinical phase:	4 years
First Patient First Visit (FPFV):	Q3/Q4 2020
Last Patient First Visit (LPFV):	Q3/Q4 2022
Last Patient Last Visit (LPLV):	Q3/Q4 2024
Trial Report Completed:	Q3/Q4 2025

The planned recruitment duration of the study is 2 years. Each patient is planned to stay at least 2 years in the study. The overall duration of the clinical phase of the trial is expected to be approximately 4 years. The actual overall duration or recruitment may vary.

See Trial Schedule on page 13 for detailed information on overall and individual duration.

5 Selection of Patients

5.1 Number of Patients and Recruitment

As described in Section 10.3, 252 patients should be randomized in the clinical trial. Following a 1:1:1:1 randomization 63 patients shall be allocated to each arm.

Recruitment and treatment of patients should be performed in 25 or more centers to recruit the intended number of patients. Expecting a number of at least 5 eligible patients per year and center, approximately 2 years are required to recruit the intended number of patients.

5.2 General Criteria for Patients' Selection

This clinical trial can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Any questions regarding a patient's eligibility should be discussed with the Coordinating Investigator or, if applicable, the Scientific Coordinator.

General: Adult patients with newly diagnosed acute myeloid leukemia who are eligible for intensive therapy may be included.

Sex: AML has been shown to be slightly more frequent in males. For gemtuzumab ozogamicin / glasdegib outcome has not been shown to be related to sex. For gemtuzumab ozogamicin contradicting results are published either supporting a relation between sex and outcome or not supporting any relation between both. However, as it has not been shown that gemtuzumab ozogamicin or glasdegib cause harm in any sex in terms of outcome, both sexes are included.

Ethnicity: AML has been shown to occur in all ethnicities without impact on outcome after correction for confounding co-variables. Neither the pharmacokinetic nor the pharmacodynamic data of gemtuzumab ozogamicin and glasdegib showed a correlation with ethnicity.

5.3 Inclusion Criteria

Trial Population - Inclusion Criteria:

- Patients with newly diagnosed CD33 positive acute myeloid leukemia according to the 2016 WHO classification
- Genetic and immunophenotypic assessment in the central laboratory
- No prior chemotherapy for leukemia except hydroxyurea to control hyperleukocytosis (≤7 days) *
- Age ≥18 years, no upper age limit
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2. See appendix 19.1
- Signed written informed consent
- Ability of patient to understand character and consequences of the clinical trial
- Non-pregnant and non-nursing women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 72 hours prior to start of study treatment. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

  Post-menopausal** or evidence of non-childbearing status is defined within this clinical trial:

  - Amenorrheic for at least **24 consecutive months** without an alternative medical cause following cessation of exogenous hormonal treatments.
  - Chemotherapy-induced menopause with >1 year interval since last menses
  - Surgical sterilisation
- WOCBP are to be advised using two effective methods of birth control to avoid pregnancy throughout the study and for at least 7 months after the last dose of GO. This includes effective contraception methods that can achieve a failure rate of less than 1% per year (e.g. hormonal contraceptive and condom, IUD/IUS and condom) or sterilization, resulting in a failure rate less than 1% per year.
- Fertile men must also be willing and able to use two effective methods of birth control (e.g latex condoms plus hormonal contraception in their partner) throughout the study and for at least 4 months after the last dose of GO, if their sexual partners are WOCBP (acceptable methods see above). A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
- For WOCBP and fertile men equally, effective contraception methods are also required during the intake of glasdegib and for at least 30 days thereafter.

5.4 Exclusion Criteria

Trial Population - Exclusion Criteria:

- AML with *PML-RARA* or *BCR-ABL1*
- Patients with known active central nervous system (CNS) leukemia (assessed clinically).
- Prior treatment with a smoothened inhibitor (SMOi) and/or hypomethylating agent (HMA) for AML. (treatment of a preceding myelodysplastic syndrome (MDS) with HMA is not an exclusion criterion.)
- Inadequate renal function: creatinine >1.5 x upper normal serum level; estimated creatinine clearance ≤30 mL/min (calculated using the standard method for the institution).
- Inadequate liver function: ALT and AST ≥2.5 x ULN), total bilirubin ≥1.5 x ULN; Alkaline phosphatase ≥2.5 x ULN. Known liver cirrhosis or history of sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD)
- Uncontrolled hypertension; severe obstructive or restrictive ventilation disorder

- Any one of the following ongoing or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, arrhythmias (including sustained ventricular tachyarrhythmia), right or left bundle branch block and bifascicular block, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF NYHA III/IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism; as well as bradycardia defined as <50 bpms
- QTc interval >470 msec using the Fridericia correction (QTcF).
- Uncontrolled infection
- Prior allo-HCT for the treatment of a condition different from AML
- Patients known to be refractory to platelet or packed red cell transfusions as per institutional guidelines, or who are known to refuse or who are likely to refuse blood product support.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancer or low grade prostate carcinoma, where an active surveillance is foreseen (Gleason Score 6, normal rectal examination, PSA <10, ≤2 positive biopsies out of 12, and less than 50% of tumorinfiltration on the examined sample). Patients are not considered to have a “currently active” malignancy if they have completed therapy for more than one year and are considered by their physician to be at less than 30% risk of relapse within one year.
- Severe neurologic or psychiatric disorder interfering with ability of giving informed consent
- Known or suspected active alcohol or drug abuse
- Known positivity for human immunodeficiency virus (HIV), active hepatitis B virus (HBV), hepatitis C virus (HCV), or hepatitis A infection
- Evidence or history of severe non-leukemia associated bleeding diathesis or coagulopathy
- Major surgery within four weeks prior to enrolment
- No consent for biobanking and for registration, storage and processing of the individual disease-characteristics and course as well as information of the family physician about study participation.
- Pregnancy and lactation
- History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product
- Participation in a clinical study involving an investigational drug(s) (Phases 1-4) within 4 weeks prior to study entry.

5.5 Reproduction Guidelines

In this study, male subjects who are potentially able to father children and female subjects who are of childbearing potential may receive gemtuzumab ozogamicin and glasdegib, which have been associated with teratogenic risk. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use two highly effective forms of contraception throughout the study and for at least 7 months (females) and 4 months (males), respectively after the last dose of GO and for 30 days after the last dose of glasdegib (females and males equally).

Male subjects are to be advised using a condom to prevent potential transmission of investigational product via seminal fluid. The investigator or his or her designee, in consultation with the subject, confirms that the subject has selected two effective methods of birth control to avoid pregnancy and confirms that the subject has been instructed in their consistent and correct use. In addition, the investigator or designee instructs the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner(s).

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the methods described in Table 1.

Table 1: Methods of Birth Control

Highly effective (failure rate <1% if used consistently and correctly) low user dependency	**Highly Effective (failure rate <1% if used consistently and correctly) high user dependency**
Progestogen only implantable contraceptive: • Intrauterine hormone releasing system (IUS) • Intrauterine device (IUD) • Bilateral tubal occlusion	Combined hormonal contraception (estrogen and progestogen): • Oral • Intravaginal • Transdermal • Injectable
Vasectomized partner: A vasectomized partner is a highly effective form of contraception provided they are the sole male partner of the WOCBP and the absence of sperm has been confirmed. If not an additional highly effective method of contraception should be used.	Progestogen only hormonal contraception • oral • injectable

5.6 Criteria for Withdrawal

5.6.1 Withdrawal of Patients

A patient must be withdrawn from the trial treatment or/and all trial-related procedures for the following reasons:

- At any time at their own request. Withdrawal of patient's consent to continue therapy. Unresolved AEs should be followed.
- Patients failing to obtain CR/CRi after induction therapy (including potential salvage therapy) or relapsing from CR/CRi during consolidation/ maintenance therapy
- Unacceptable toxicity necessitating cessation of treatment
- Changes in medical status of the patient such that the investigator believes that patient safety is compromised or that it would be in the best interest of the patient to stop treatment
- Pregnancy
- Non-compliance by the patient with protocol requirements
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome if possible.

If the patient withdraws from the trial and also withdraws consent for disclosure of future information (e.g. follow-up visits), no further evaluation is allowed to be performed and no additional data is collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

5.6.2 Handling of Withdrawals

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the patient's medical records. In case of withdrawal of a patient at his/ her own request, the reason should be asked for as extensively as possible and documented.

5.6.3 Replacement of Patients

Randomized patients who do not receive induction therapy with gemtuzumab ozogamicin for any reasons are replaced. All patients receiving at least one dose of the IMP gemtuzumab ozogamicin are not replaced.

5.6.4 Premature Closure of the Clinical Trial or a Single Center

The trial can be prematurely closed or suspended by the Sponsor after consulting the Coordinating Investigator. The Ethics Committee (EC) and the competent regulatory authorities must then be informed. Furthermore, the Ethics Committee(s) and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (investigational medicinal product and other material not required to remain at the site) must be returned to the Sponsor in Heidelberg or treated according to Sponsor's instructions.

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial centers and investigators.

The Sponsor after consulting the Coordinating Investigator has the right to close a center, at any time, in case of:

- Non-compliance with the protocol
- Poor data quality
- No recruitment in 6 months

5.7 Prior and Concomitant Illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and are documented on the appropriate forms of the electronical case report form (eCRF). Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate forms of the eCRF (see Section 9.1.1).

5.8 Background Medication

As background therapy, the patients receive Daunorubicin during induction therapy as well as Cytarabine during induction and consolidation therapy.

See Section 6.3 for the details on the administration schedule.

5.9 Prior and Concomitant Medication / Non-Drug Treatment

All concomitant medications and treatments must be recorded in the CRF. Any prior treatment received within 28 days prior to start of study treatment (including hematopoietic growth factor receptor agonists: erythropoietin, (G-CSF), romiplostim, eltrombopag) are to be recorded in the CRF.

Every concomitant treatment, blood products, any transfusion (red blood cells or platelets), growth factors, as well as interventions, required by the patients during the active study treatment (and up to 28 days following last study drug administration or until initiation of another anti-cancer treatment) and the reason for its administration must be recorded on the CRF.

All concomitant medications the patient is currently receiving must be reviewed by the Investigator prior to enrollment.

5.9.1 Restricted or Prohibited Concomitant Medications

The following medications are not allowed during the active study consolidation and maintenance period:

- Erythropoietin or darbepoietin;
- Thrombopoietin receptor agonists (e.g., eltrombopag, romiplostim);
- Hydroxyurea or other anti-cancer agents (e.g., hormones, cytokines, etc.);
- Investigational agents for the treatment of hematologic malignancies;
- **CYP3A4/5 Inducers**: glasdegib metabolism may be induced when taking CYP3A4/5 inducers, resulting in reduced plasma concentrations. The impact of CYP3A4/5 inducers on glasdegib pharmacokinetics has not been studied in the clinic. Therefore co-administration of glasdegib with any of the following and other moderate/strong CYP3A4/5 inducers is not permitted (unless approved by the principle investigator or the scientific coordinator) from study entry until study treatment discontinuation (tacrolimus, avasimibe, mitotane, phenytoin, enzalutamide, semagacestat, bosentan, genistein, thioradazine, nafcillin, modafinil, carbamazepine, phenobarbital, phenytoin, rifampin, rifabutin, rifapentine, St. John's Wort). In case of uncertainty whether a concomitant medication is contraindicated, the principle investigator or the scientific coordinator should be contacted.

The following medications have use restrictions during the active study consolidation and maintenance period:

- Aspirin in doses exceeding 300 mg per day is not permitted.
- Oral anticoagulation with warfarin is not recommended if alternative medication (e.g., low molecular weight heparin) can be substituted as per investigator judgment. If warfarin is indispensable, frequent monitoring of the International Normalized Ratio (INR) is recommended and the dosage of oral anticoagulant should be adjusted as needed.
- **CYP3A4/5 Inhibitors**: In vitro studies with human liver microsomes and recombinant CYP enzymes indicated that glasdegib metabolism is primarily mediated by the drug-metabolizing enzyme CYP3A4/5. Clinically, there is likelihood that glasdegib plasma concentrations may be increased in the presence of co-administered inhibitors of the CYP3A4/5 enzymes. In a healthy volunteer study, ketoconazole, a potent CYP3A4/5 inhibitor, produced a 2.4-fold increase in plasma exposure and a 1.4-fold increase in peak plasma concentration of glasdegib. Tacrolimus, a potent immunosuppressive drug, known to be metabolized predominantly in the liver by cytochrome P450 3A (CYP3A) in coadministration with glasdegib, significantly increases the risk of AEs, including QTc interval prolongation.Therefore, a potential exists for drug-drug interactions with CYP3A4/5 inhibitors, and co-administration of glasdegib in combination with moderate/strong CYP3A4/5 inhibitors is not recommended. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Moderate/strong CYP3A4/5 inhibitors should be used with caution and only if considered medically necessary.
- Surgery: Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and glasdegib required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping glasdegib is recommended at least 7 days prior to surgery. Post-operative reinitiation of glasdegib treatment is basically at the Investigator's discretion but requires approval of the principle investigator or the scientific coordinator and should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6 Investigational Medicinal Products

6.1 Gemtuzumab Ozogamicin

6.1.1 General Information

Investigational medicinal product:

Drug Code:	PF-05208747
International Nonproprietary Name (INN):	Gemtuzumab ozogamicin
ATC code, if officially registered:	L01XC05
Pharmaceutical formulation:	20 mL ampoules of 5 mg (Mylotarg®, commercially available drug is used)
Route of administration:	Intravenous
Storage conditions:	+2 to +8°C, protect against light
Manufacturer / Importer:	Pfizer Pharma GmbH
License Number	EMEA/H/C/004204

6.1.2 Summary of Gemtuzumab Ozogamicin Product Profile

Gemtuzumab ozogamicin (GO), an antibody-conjugated chemotherapy agent, is a conjugate of a derivative of calicheamicin, a cytotoxic agent, linked to a recombinant humanized antibody (hP67.6) against the hematopoietic antigen targeted by GO (CD33).

GO has been initially developed as monotherapy for the treatment of patients ≥60 years of age who have CD33-positive AML in first relapse and who are not otherwise candidates for cytotoxic chemotherapy. Based on this indication GO was approved in several countries including the United States but not in Europe. Approval in the US under Subpart H required conversion to full approval based on submission of additional data to confirm clinical benefit. Consequent to the failure of the nominated confirmatory study (SWOG S0106) and in the absence of other equivalent data, FDA recommended and Pfizer agreed to the voluntary withdrawal of the US NDA (New Drug Application), effective 15 October 2010.

Since then, numerous publications from Investigator-Initiated Research studies (IIR) have suggested that GO (at lower and fractionated doses) may be administered safely in combination with daunorubicin + cytarabine and this combination may provide significant clinical benefit to AML patients. Based on the results obtained from those studies Pfizer received regulatory approval for GO in combination with daunorubicin and cytarabine for the treatment of previously untreated CD33 positive AML. GO has been re-approved by the FDA in September 2017 and received a marketing authorization by the EMA on 19 April 2018.

Complete information for GO is laid down in the applicable Investigator Brochure (IB).

6.1.3 Known Side Effects

An important toxicity associated with GO is hepatotoxicity including sinusoidal obstructive syndrome (SOS) which can be fatal and is also known as hepatic veno-occlusive disease (VOD).

Other serious toxicities associated with GO include infusion related reactions, myelosuppression, infection, hemorrhage, tumor lysis syndrome.

Common side effects of administration include shivering, nausea, and fever.

When GO is given in combination with standard cytotoxic chemotherapy regimens for first line in AML, a similar toxicity profile as seen with monotherapy is observed with combination therapies.

More detailed information on the efficacy and safety of GO are laid down in the applicable Investigator Brochure (IB).

6.2 Glasdegib

6.2.1 General Information

Investigational medicinal product:

Drug Code:	PF-04449913
International Nonproprietary Name (INN):	Glasdegib
ATC code, if officially registered:	L01XX63
Pharmaceutical formulation:	100 mg tablets, 25 mg tablets (Daurismo®, clinical study supplies are used)
Route of administration:	administered orally once daily
Storage conditions:	+15 to +30°C, in a dry environment
Manufacturer / Importer:	Pfizer Pharma GmbH
License Number	EMEA/H/C/004878

6.2.2 Summary of Glasdegib Product Profile

Glasdegib is a potent and selective inhibitor of the Hh signaling pathway through binding to its target SMO. It is currently being developed for the treatment of hematologic malignancies.

Complete information for glasdegib is laid down in the applicable Investigator Brochure (IB).

Clinical study supplies of glasdegib and matching placebo are made available by Pfizer.

EU-approval of glasdegib (Daurismo®) was granted in June 2020.

6.2.3 Preclinical Toxicity Data

Glasdegib has been extensively characterized in nonclinical safety studies in rats, dogs and rabbits. The primary target organs in rat included kidney, bone, and tooth.

Additional observations of alopecia and skin irritation/inflammation, and QTc prolongation were identified in dogs. Glasdegib was teratogenic at all doses tested in rats and rabbits.

6.2.3.1 Clinical Relevance of Organ Toxicities Observed in Nonclinical studies

In general, many findings in rats and dogs predict drug reactions reported in the clinic with glasdegib; these include muscle spasms, alopecia and QTc prolongation. However, not all of the organ toxicities observed in animals have been observed in humans when treated with glasdegib.

6.2.4 Known Side Effects

Glasdegib has been tested in humans in several studies. One hundred twenty-nine (129) treatment-related SAEs were reported in 66 patients. Of those the most frequently reported events (in ≥2 patients) included febrile neutropenia (18 events), pneumonia (6 events), fatigue (5 events), anemia (4 events), gastrointestinal hemorrhage, nausea, vomiting, device related infection, sepsis (3 events each), acute kidney injury, acute myocardial infarction, sudden death, edema peripheral, clostridium difficile infection, dehydration, bacteremia, pre-syncope, electrocardiogram QT prolonged, myalgia, polyneuropathy, pyrexia, and thrombocytopenia (2 events each).

The following treatment related SAEs were reported in 2 or more patients after being treated with glasdegib.

Table 2: treatment related SAEs reported in ≥2 patients

Preferred Event Term	Study Drug	Totals
Febrile neutropenia	18	18
Pneumonia	6	6
Fatigue	5	5
Anaemia	4	4
Device related infection	3	3
Gastrointestinal haemorrhage	3	3
Nausea	3	3
Sepsis	3	3
Vomiting	3	3
Acute kidney injury	2	2
Acute myocardial infarction	2	2
Bacteraemia	2	2
Clostridium difficile infection	2	2
Dehydration	2	2
Electrocardiogram QT prolonged	2	2
Myalgia	2	2
Oedema peripheral	2	2
Polyneuropathy	2	2
Presyncope	2	2
Pyrexia	2	2
Sudden death	2	2
Thrombocytopenia	2	2

Source: Excel IB 03-JAN-2017 GLASDEGIB, Treatment-related PT Frequency.
Data cutoff date: 03 January 2017

Eleven patients died due to SAEs that were judged study treatment (glasdegib and/or backbone chemotherapy) related.

More detailed information on the efficacy and safety of glasdegib is available in the applicable Investigator Brochure (IB).

6.3 Dosage Schedule & Treatment plan

Induction therapy (1 cycle):

Arm	Type	Drug	Administration	Days
all	SOC	Cytarabine	200mg*/m², i.v. continuously	1 to 7
all	SOC	Daunorubicin	60mg/m², i.v. 1h infusion	1, 2,3
GO-147	IMP	Gemtuzumab Ozogamicin	3mg/m² (cap at 5mg absolute), i.v. 2h infusion (Mylotarg®).	1, 4, 7
GO-1	IMP	Gemtuzumab Ozogamicin	3mg/m² (cap at 5mg absolute), i.v. 2h infusion (Mylotarg®)	1

*In patients older than 70 years of age dose reduction to 100mg/m² on an optional basis.

Conditional salvage therapy (1 cycle, optionally):

In case of day 15 bone marrow blast count >10% or no CR/CRi after the induction cycle, one cycle of high-dose cytarabine and mitoxantrone (HAM) is allowed within the protocol.

Arm	Type	Drug	Administration	Days
All	SOC	Cytarabine	1g/m², i.v. 2h infusion, twice daily	1, 2, 3
All	SOC	Mitoxantrone	10mg/m², i.v. 30 minutes infusion	2, 3

Patients failing to obtain CR/CRi after induction therapy (including potential salvage therapy) are to be withdrawn from study treatment.

Consolidation therapy (2 cycles):

Arm	Type	Drug	Administration	Days
All	SOC	Cytarabine	1g/m², i.v. 3h infusion twice daily	1, 2, 3
Experimental	IMP	Glasdegib	100mg, tablet	1 to 28
Standard	---	Placebo	100mg, tablet	1 to 28

Maintenance therapy (6 cycles):

Arm	Type	Drug	Administration	Days
Experimental	IMP	Glasdegib*	100mg, tablet	1 to 28
Standard	SOC	$SOC^{PhC\#}$	as per SmPC	1 to 28

*switch to SOC^{PhC} feasible at any time, #optional, not stipulated within the scope of study treatment

Patients relapsing from CR/CRi during consolidation or maintenance therapy are to be withdrawn from study treatment.

6.3.1 Dosage Adjustment

Every effort should be made to administer the study drug treatment according to the planned dose and schedule.

In the event of significant toxicity, dosing must be interrupted, delayed and/or reduced as outlined below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients must be instructed to notify investigators at the first occurrence of any adverse symptom/s.

For **gemtuzumab ozogamicin** dose modifications in the GO-147 schedule: In case of CTC grade ≤2 toxicity due to gemtuzumab ozogamicin on day 1 or day 4 proceeding to subsequent administration (day 4 or day 7) is allowed. In case of grade 3 toxicity on day 1 or 4, patients can only proceed to day 4 and 7 administration if the CTC grade has improved to < grade 3 toxicity. In case of CTC grade 4 toxicity, gemtuzumab ozogamicin is to be discontinued. Likewise, patients who develop anaphylaxis, pulmonary edema, acute respiratory distress syndrome or SOS after the first administration are not allowed to receive further doses of GO.

For **glasdegib (or placebo)** dose should be modified in the event of Grade 3 or Grade 4 non-hematologic, study-treatment-related toxicity, whereas dosing may be delayed and/or reduced. The glasdegib dose should be reduced stepwise by 1 dose level per step, i.e. in decrements of 25 mg (75 mg QD, 50 mg QD, and 25 mg QD, translating into 3, 2, or 1 x 25 mg tablets respectively).

Glasdegib or placebo does not need to be delayed or dose reduced for hematologic study-treatment-related toxicity during consolidation therapy exept in case of ANC <100/mm³ and /or platelets <10,000/mm³ irrespective of the time of occurrence.

If there is a need to deviate from any of the dose modifications this first must be discussed with the Coordinating Investigator.

Table 3: Dose Modifications for Non Hematologic Toxicities

Toxicity (NCI CTCAE version 5.00)	Glasdegib Dose modification
Renal Toxicity: Serum creatinine or BUN ≥2x above baseline value or serum bicarbonate level <20 mmol/L	Hold until toxicity has recovered to ≤Grade 1 First episode: Decrease by 1 dose level Second episode: Decrease by 1 dose level Third episode: Permanently discontinue
Other Non-Hematologic Toxicities (Excluding QTc Prolongation, Muscle Spasms and Myalgia): ≥Grade 3 toxicity (Nausea, vomiting, and/or diarrhea must persist at ≥Grade 3 (despite maximal appropriate medical therapy) to require dose modification)	Hold until toxicity has recovered to ≤Grade 1 First episode: Decrease by 1 dose level Second episode: Decrease by 1 dose level Third episode: Permanently discontinue

Table 4: Glasdegib/placebo Dose Modifications for mean QTcF (mQTcF)

CTCAE	Grade 1	Grade 2	Grade 3**	Grade 4
Electrocardiogram QT corrected (QTc) interval prolonged *	450-480 msec	481-500 msec	≥501 msec at least two separate ECGs	QTc >= 501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

*The severity of QTc prolongation assessment is to be done by calculating a mean QT of 3 consecutive ECGs performed approximately 2 minutes (but no longer than 5 minutes) apart by using the Fridericia correction method (mQTcF).
** If mQTcF is ≥501 msec continuous ECG monitoring and cardiology consultation are required.

		Grade			
Category	Requirement	1	2	3	4
ECG monitoring	Continuous ECG monitoring and cardiology consultation for mQTcF ≥501 msec			x	x
Initial PF 04449913 action	Discontinue and do not re-challenge.				x
	Interrupt treatment		x	x	
	Continue at same level	x			
General management	Assess for and correct electrolyte abnormalities.	x	x	x	x
	Withhold any concomitant medications if possible that may cause QTc prolongation.		x	x	x
Resume PF 04449913 dosing	At prior dose if mQTcF returns to ≤470 msec and to within 20 msec of baseline in 7 days and if no prior dose interruption related to mQTcF prolongation has occurred		x	x	
	At one lower dose level if mQTcF returns to ≤470msec and to within 20 msec of baseline between 7-14 days. and if no prior dose interruption related to mQTcF prolongation has occurred		x	x	
	At one lower dose level if mQTcF returns to ≤470 msec and to within 20 msec of baseline in 14 days if one prior dosing interruption related to mQTcF prolongation has occurred		x		
Management after dose resumed	An ECG should be repeated and mQTcF re-assessed approximately 7 days after PF-04449913 dosing resumption following interruption for a mQTcF prolongation		x	x	
Discontinue PF-04449913 permanently	The mQTcF prolongation does not return to≤470 msec and to within 20 msec of baseline after 14 days		x	x	
	The Grade ≥2 mQTcF prolongation recurs after one dose reduction related to mQTcF prolongation		x	x	
	The Grade ≥3 mQTcF prolongation recurs after one prior dosing interruption related to mQTcF prolongation has occurred			x	
	If at any time during the 14 day window that PF 04449913 is stopped due to QTcF prolongation the patient has a confirmed mean QTcF interval >515 msec or becomes symptomatic		x	x	

"PF 04449913" = glasdegib

6.3.2 Dosage Interruptions

Glasdegib patients should have their treatment interrupted when

- Experiencing Grade 3 or 4 toxicities **potentially attributable to glasdegib** regardless of when it occurs in the cycle until the toxicity resolves or returns to baseline.
- ANC <100/mm^3 and /or platelets <10,000/mm^3 regardless of when it occurs in the cycle until
    - Hematologic toxicities: ANC ≥100/mm^3 and platelet count ≥10,000/mm^3, provided that re-treatment can occur safely as per the Investigator's judgment.
    - Non-hematologic toxicities listed in Table 3 have returned to baseline or ≤Grade 1 severity.

Appropriate follow-up assessments should be implemented until adequate recovery (toxicity resolves or returns to baseline) occurs.

- If these conditions are met within ≤21 days of dose interruption, glasdegib may be resumed (see Section 6.3.1) for AEs requiring dose reduction at the time of treatment resumption).
- If these parameters have not been met following >21 days of dose interruption, permanent discontinuation of treatment with glasdegib should be considered.

Depending on when the adverse event resolved, treatment interruption may lead to the patient missing all subsequent planned doses of glasdegib within the cycle. If the AE leading to treatment interruption recovers within the same cycle, re-commencement of dosing in that cycle is allowed. Glasdegib doses omitted for toxicity are not replaced within that cycle (e.g., cycles are not to be prolonged beyond 28 days in order to make up for any missed glasdegib doses during that cycle).

The need for a dose reduction at the time of treatment resumption should be based on the criteria outlined in Section 6.3.1, unless specifically agreed otherwise following discussion between the Investigator and the Sponsor. In the event of glasdegib treatment interruption for reasons other than treatment-related toxicity (e.g. elective surgery) for a duration of >21 days, the details of treatment resumption are determined in consultation with the Coordinating Investigator.

QTcF Interval Monitoring and Management: Patients should be closely monitored for potential cardiovascular symptoms. Appropriate monitoring should include clinical examinations, vital signs, routine ECGs, and AE monitoring. In case of QTc prolongation, concomitant conditions such as electrolyte imbalances, hypoxia, or use of medications affecting the QT interval should be ruled out or corrected. In case of clinically significant toxicities, glasdegib administration should be interrupted and the dose reduced as indicated in Table 4Table 4.

6.3.3 Administration of Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin: gemtuzumab ozogamicin should be stored refrigerated at 2°C to 8°C and protected from light. The lyophilized substance may only be used until the expiration date provided on the vial. Following reconstitution of 5 mg to a dose of 1 mg/mL, the reconstituted solution should be diluted in NaCl 0.9% (final concentration between 0.075 mg/ml and 0.234 mg/ml).

Gemtuzumab ozogamicin should be administered as a two hour intravenous infusion

6.3.4 Administration of Glasdegib

Glasdegib is administered in up to 28-day cycles. Cycle duration maybe extended beyond 28 days to allow resolution of toxicities related to study treatments. It is suggested that sites contact the patients via phone during the first week of glasdegib Cycle 1 and anytime there is a dose reduction to confirm that the patient adequately understands the dosing instructions.

Glasdegib is self-administered by the patient at home, unless otherwise specified. Glasdegib is administered orally with approximately 8 ounces (240 mL) of water and should be taken in the morning, at the same time each day. Tablets must not be crushed or cut; they must be swallowed whole, not manipulated or not chewed prior to swallowing. Patients should be instructed to self-administer their medication in the morning at approximately the same time each day and to not take more than the prescribed dose at any time.

If a patient forgets to take his/her dose at the regularly scheduled time, and if less than 10 hours have passed since the scheduled dosing time, that dose should be taken as soon as possible. If more than 10 hours have passed since the scheduled dosing time, the dose should be skipped and the patient should continue on their normal dosing schedule. If a patient misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a patient vomits any time after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed.

If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of glasdegib. The patient is reminded NOT to take their dose at home on clinic days but to bring their bottle(s) and patient dosing diary into clinic so that glasdegib may be administered there. The visits must be scheduled in accordance to the 10h window described above.

Patients requiring glasdegib dose reduction(s) are administered multiples of 25 mg tablets and should continue taking glasdegib at the same time each morning at the dose prescribed by the Investigator (i.e., 75 mg QD and 50 mg QD in the form of three or two 25 mg tablets respectively). In situations where clinical benefit is observed, glasdegib can be reduced below 50 mg QD upon Sponsor approval.

6.4 Drug Supplies, Formulation, Labelling and Storage

6.4.1 General Aspects

Supplies of both IMPs are shipped by Pfizer Worldwide Research and Development to one sponsor-authorized central distribution unit (“coordinating pharmacy”) providing local pharmacies or study sites with required amounts of the investigational medicinal product. A pre-requisite for shipment is the full regulatory approval of the study site.

The local pharmacies of the participating centers keep accounts of the trial medication and acknowledge the receipt of all shipments of the trial medication. Adequate records on receipt, use, return, loss, or other disposition of medication must be maintained. A specific drug accountability form either supplied or approved by the Sponsor has to be used to provide drug accountability information. Information describing study drug supplies and their disposition, patient by patient, must be provided, signed by the Investigator and returned to the NCT clinical trials office. Requisite data includes relevant dates, quantities, batches or code numbers, and patient identification for patients who received trial product.

The investigator also keeps accurate records of the quantities of trial medication dispensed, used, and returned by each patient. The documentation has to include date of dispensary, patient identification, batch/ serial numbers or other identification of trial medication. At the end of the trial, all unused trial medication and all medication containers are destroyed and this process takes place and is documented at the local pharmacy. Trial medication that may no longer be used (e.g. expiry date passed) may be destroyed before the end of the trial. If destruction of trial medication at the site is not possible, it may be sent to the sponsor for destruction. It is assured that a final report of the drug accountability is prepared and maintained by the investigator in the Investigator’s site file.

All trial medication must be kept in a locked area with access restricted to designated trial staff. The trial medication must be stored dry and in accordance with manufacturer’s instructions. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once a temperature excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion.

Site staff instructs patients on the storage requirements for take home medications including how to report temperature excursions.

The IMPs are not allowed to be used outside the context of this protocol. Under no circumstances should the Investigator or site personnel supply study product to other investigators or clinics, or allow the supplies to be used other than as directed by this protocol.

6.4.2 Gemtuzumab Ozogamicin

Commercially labeled bottles of GO (Mylotarg®) are supplied by Pfizer Worldwide Research and Development as vials containing 5mg for intravenous infusion. Supplies are labeled by the Sponsor or a delegate according to local regulatory requirements.

Investigational product should be prepared and administered by an appropriately qualified and experienced member of the study staff as allowed by local, state, and institutional guidance.

6.4.3 Glasdegib/Placebo

Clinical study supplies of glasdegib and matching placebo are made available by Pfizer Worldwide Research and Development as 100 mg and 25 mg tablets for oral administration. Supplies are labeled by the Sponsor or a delegate according to local regulatory requirements.

Glasdegib and matching placebo are packaged in high-density polyethylene (HDPE) bottles and should be handled with care. Each bottle contains enough medication for a 28-day cycle of daily dosing, plus an additional amount to cover the time between site visits. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other containers and return the bottles to the site at the next study visit. Site personnel must ensure that patients clearly understand the directions for self-medication.

Investigational product should be dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

6.5 Compliance

Gemtuzumab ozogamicin is administered on site as intravenous infusion.

For **glasdegib**/**placebo**, all patients maintain patient dosing diaries throughout the study recording dates of administration and all regular, missed, changed, or delayed doses.

Patients are required to return all bottles, unused study drug and the patient dosing diary, after each cycle and at EOT visit for compliance assessment and drug accountability. The number of tablets returned by the patient at the end of the cycle is counted, documented and recorded.

7 Trial Methods

7.1 Patient Registration and Randomization

The informed consent has to be signed before enrollment into the study i.e. it must be signed prior to any trial-related procedures including initiation of therapy.

Each patient having signed informed consent and meeting all inclusion criteria must be registered. Prior to this, each patient intended to be registered must be allotted a screening number by the study site (usually ascending numbers beginning from 1).

Patients are registered through the eCRF (or per fax registration in case of technical failures) and the unique patient ID (PAT-ID) is assigned via the registration process. The PAT-ID is composed of the aforementioned screening number and the site number.

Following registration the patient is randomized into one of the study arms and is allotted to a randomization number (Rand-No) in addition to the PAT-ID. Randomization is done using a centralized web-based tool (www.randomizer.at) by which randomization for double-blind clinical trials can easily be handled.

Patients withdrawn from the trial retain their identification codes (Rand-No and/or PAT-ID, if already given). New patients must always be allotted a new identification code.

For assistance, contact the NCT Clinical Trials Office (see responsibilities page 2).

7.1.1 Randomization Procedure and Blinding

Eligible patients are randomized in a concealed fashion to one of the four treatment arms in a 1:1:1:1 ratio. Randomization is performed stratified by age (≤70 years vs. >70 years) and ECOG performance status (ECOG PS = 0 vs. ECOG PS >0), both of which are assumed to be the most important prognostic factors. Block randomization with varying block length is performed to achieve balanced group sizes per stratum. Due to the small number of expected patients per center, randomization is not stratified per center in order to avoid the risk of an unbalanced number of patients between the treatment arms. Instead, “center” is taken into account as a random factor in the statistical model (see Section 10.5 for details).

Study–medication tablets (glasdegib/placebo) are blinded to patients and investigators until the end of consolidation therapy. Prior to starting maintenance therapy (i.e. after consolidation therapy) all patients are unblinded. Patients randomized to the placebo–arm are offered switching to standard of care according to Physician’s Choice (SOC^{PhC}), whereas patients of the glasdegib-arm can either continue with glasdegib treatment for up to 6 months or switch to SOC^{PhC}.

Trial personnel, to whom patient treatment during maintenance is not necessarily to be disclosed, including biometricians, shall remain blinded from the time of randomization until database lock.

Detailed instructions on randomization, blinding and breaking the blind are distributed to the respective authorized personnel prior to the start of the study.

7.2 Description of Study Visits

A detailed description of study visits via day-by day flowcharts is given in appendix 19.4.

7.3 Methods of Data and Sample Collection

7.3.1 Data Collection and Handling

All data assessed as per the present protocol including clinical and laboratory data are documented by the investigator or an authorized member of the study team in the patient's medical record and in the electronic case report form (eCRF). The investigator at the clinical site is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified against source data. The eCRF has to be filled out according to the specified eCRF Completion Guidelines. The correctness of entries in the eCRF is confirmed by dated elec–tronic signature of the responsible investigator. All data are reported in a pseudonymized manner.

7.3.2 Sample Collection and Handling (Bone Marrow and Peripheral Blood)

For central review and translational analysis following samples are necessary:

Bone marrow (BM)	Peripheral blood (PB)
• 4 unstained bone marrow slides (reference morphology) • BM aspirate, 20 mL, Heparin • BM aspirate, 10 mL, EDTA (first pull if feasible) • At baseline only: bone marrow biopsy optionally in formalin • At baseline only: Bone marrow aspirate, 10 ml, EDTA additionally (20ml in total)	• 2 PB smears • PB, Heparin (40 mL at baseline/initial diagnosis, 10 mL during follow-up)

In case of punctio sicca and presence of peripheral blasts, bone marrow diagnostics can also be done from peripheral blood. If there is another reason why bone marrow diagnostics cannot be performed, the principal investigator or the medical coordinator should be contacted.

The samples are collected at the following days:

- Baseline:
- Day 15 optional sample, can alternatively be taken 1 day earlier or up to 3 days later (i.e. at day 14/16/17/18) if medically indicated (e.g. to avoid arrival of samples at the central lab on Saturday/Sunday)
- One sample between day 28 – 42 (remission status assessment after induction therapy)
- Remission status assessment after each consolidation therapy cycle
- Remission status assessment at three months of and after maintenance therapy (EOT)
- During follow-up every three months until 2 years from day 1 or longer and at end of follow-up (EOS)

All samples are shipped to the Central MRD Laboratory.

Shipment address: see “Central MRD laboratory” under “Responsibilities”, page 2.

Transport is done by courier service or a similar operator ensuring the needed transport conditions. Until shipment the samples may be stored at room temperature (max 22°C).

Overview Bone Marrow (BM) and Peripheral Blood (PB) Samples

No.	Visit/ Cycle	BM slides	BM aspirate	PB	PB smear
1	IT: Baseline	5	30 mL	50 mL	2
2	IT: Day 15 (optional)	4	30 mL	10 mL	2
3	IT: between day 28-42	4	30 mL	10 mL	2
4	End CT cycle 1	4	30 mL	10 mL	2
5	End CT cycle 2	4	30 mL	10 mL	2
6	End MT cycle 3	4	30 mL	10 mL	2
7	EnD MT cycle 6 (EOT)	4	30 mL	10 mL	2
8	FU month 3	4	30 mL	10 mL	2
9	FU month 6	4	30 mL	10 mL	2
10	FU month 9	4	30 mL	10 mL	2
11	FU month 12	4	30 mL	10 mL	2
12	End of follow-up (EOS)	4	30 mL	10 mL	2
	Subtotal	**45/49**	**330/360 mL**	**140/150 mL**	**22/24**
	Additional / optional				
13	FU year 2	4	30 mL	10 mL	2
14	FU year 3	4	30 mL	10 mL	2
	Subtotal	8	60 mL	20 mL	4
	Total	**48-57**	**330-420 mL**	**140-170 mL**	**22-28**

7.4 Measurement of Efficacy Parameters

Efficacy assessments are based on analyses of complete blood cell count (CBC), bone marrow aspirate, peripheral blood and patient reported outcomes (PROs) and moreover, for patients with extramedullary disease, on clinical examination (presence of palpable lesions) and/or tumor imaging (see Section 7.4.3).

7.4.1 Hematology

Hematology (CBC including red blood cells, platelets, white blood cells with differential cell counts) is performed at baseline, at days 1, 4, 7 and 8 and then weekly during and at the end of induction therapy. Hematology is also done weekly during and after each cycle of conduction therapy, as well as at end of each cycle of maintenance therapy (plus EOT, if applicable), monthly during safety follow-up and every three months during the remaining follow-up period (plus EOS, if applicable). With regard to hematological assessments during salvage therapy (potentially added after the induction cycle) see applicable schedule on page 15.

Apart from time points of MRD assessments and values during Safety Follow-up (SA) and at day 1 of Salvage Therapy (if applicable), hematology values are collected for safety reasons and are not necessarily captured in the eCRF(see section 0).

7.4.2 Bone Marrow Aspirate and Peripheral Blood

BM aspirate and peripheral samples blood are collected at baseline, at day 15 of induction therapy on an optional basis, and at hematological recovery after induction and consolidation therapy cycles for disease assessment as well as every three months during maintenance therapy and follow-up (plus EOT and EOS, if applicable).

7.4.3 Extramedullary Disease Assessment

For all patients, extramedullary disease status is to be documented in the eCRF, in terms of presence/absence of the disease, at baseline. The site of involvement is also reported in the eCRF. During the study the extramedullary status should always be re-evaluated by the time of bone marrow evaluation (apart from day 15 of induction therapy).

Palpable lesions can be assessed by clinical examination both at baseline and during the study. Disappearance of any palpable lesion should always be confirmed by imaging-based techniques (sonographic, MRI, or CT-scan if available by clinical routine). Non-palpable lesions assessed at baseline by imaging-based techniques should be followed on study using the same technique. Baseline tumor imaging is accepted within 4 weeks prior to the start of treatment. All patients' files and radiological results must be available for source data verification.

7.4.4 Definition of Response: Disease Status AML

The response to treatment is evaluated using standard criteria defined by the European LeukemiaNet Recommendation (see Appendix 19.2) [4].

7.4.5 Monitoring of Measurable Residual Disease

For MRD assessment, BM aspirate and peripheral blood are analyzed by multi-parameter flow cytometry at the Central MRD Laboratory. Apart from day 15 of induction therapy, After the baseline assessment MRD assessments are made according to BM sampling dates as described in Section 7.3.2. As routinely performed, initial Next-Generation-Sequencing analyses of well-established targets as well as MRD monitoring is done by multiparameter flow cytometry in the Central MRD Laboratory. In parallel, MRD is evaluated in an explorative manner using a molecular biological approach.

In case of contradictory results, those obtained from the bone marrow aspirate are decisive to determine MRD negativity.

7.4.6 Patient Reported Outcomes (PROs)

PROs are assessed using paper based questionnaires of the EORTC Quality of Life Item Library (core questionnaire QLQ-C30, fatigue module QLQ-FA12, and selected symptom items), as well as the PSQI (sleep), the PHQ-4 (anxiety and depression), and the FACT-cog (cognitive function), which are handed out at the study site or mailed to the patients at regular intervals and requested to be completed.

Health economic analyses (see Section 7.5) include a secondary mapping study between the "SF-36" generic instrument and the cancer specific quality of life instrument (EORTC QLQ-C30).

7.4.7 Survival Follow-up

Survival follow-up is performed during 3-monthly observational follow-up visits starting from last visit of maintenance therapy until EOS or remotely by contacting the patient's general practitioner after achieving 2 years follow-up.

7.5 Health Economic assessments

Health care resource utilization is assessed by a case specific resource utilization questionnaire that is adjusted to the research objectives, based on clinician input, and considering data captured by the eCRF. This questionnaire is to be self-administered by the patients at the end of each cycle and 3-monthly during maintenance therapy. It includes measurements of procedures during hospital care, emergency unit admissions, consultations with specialists, general practitioner visits, concomitant medication use, and other health care resource utilization incurred during the cycle.

With regard to the use SF-36 questionnaires see Section 7.4.6.

7.6 Measurement of Safety Parameters

7.6.1 Adverse Events (AEs)

Assessment of AEs include the type, incidence, severity (graded by the NCI CTCAE version 5.0) timing, seriousness, and relatedness to study treatment. Additional information regarding AE and Serious AE (SAE) reporting is provided in Section 9.

Laboratory Safety Assessments

Hematology, blood chemistry, coagulation and urinalysis assessments are drawn at the time points described in the Trial Schedule on page 13 and are analyzed by the site/Investigator at local laboratories. Laboratory certifications and normal ranges with units must be provided to the Coordinating Investigator.

If hematology (CBC with differentials) is obtained within 3 days of a scheduled blood draw, the collection needs not be repeated. For those patients achieving complete or partial hematological response, a CBC should be done at least 4 weeks after the BM assessment in order to confirm response. Hematology tests may be repeated also as clinically indicated.

If blood chemistry or coagulations are obtained within 3 days of a scheduled blood draw, the collection need not be repeated.

If a urinalysis was obtained within 2 days of the scheduled collection, it should not be repeated. For urinalysis, dipstick is acceptable. Microscopic analyses should be done in case of abnormal results (i.e., the presence of protein or blood).

Laboratory values that are collected for safety reasons only are not captured as such in the eCRF. If significantly deviating from normal range, and/or assessed by the investigator as clinically relevant, results of safety lab investigations are to be documented as adverses events (AEs) on the appropriate forms of the eCRF (see Section 9.1.1).

Applicable reminders to the investigators will be included in the eCRF (i.e. at time points when safety lab investigations are stipulated by the study protocol, investigators will be requested to review lab results and consider if representing AEs or not).

7.7 Measurement of Further Parameters

Pharmacokinetics and pharmacodynamics are not analyzed.

7.7.1 Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, is performed regularly. Following a negative pregnancy result at screening, appropriate contraception must be commenced (see Section 5.5) and a further negative pregnancy result is then required before the patient may receive the investigational product. Pregnancy tests are also routinely repeated (see Trial Schedule page 13) during the active treatment period, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient is withdrawn from administration of study drug combination and enters into the Follow-up phase. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards (IRBs)/Ethic Committees (ECs) or if required by local regulations.

8 Ancillary and Post Trial Care

The period of treatment ends with the last visit of the sixth cycle of the maintenance therapy (EOT). After EOT patients are routinely followed-up and treated regarding standard of care according to the discretion of the treating physician. The period of observation (and the study) ends for all patients when the last patient being included and alive has been followed for at least 730 days (2 years) counted from this patient's day 1 (EOS).

8.1 Study Alliance Leukemia (SAL)

All investigators are highly encouraged to registers their AML-patients at the Study alliance Leukemia (SAL) registry, which facilitates access to further clinical AML-trials and collects structured follow-up data. For further information please refer to https://www.sal-aml.org/ or contact:

Prof. Dr. med. Christoph Röllig, MSc
Head of the SAL Trial Center
Medizinische Klinik und Poliklinik I
Universitätsklinikum Carl Gustav Carus Dresden
Fetscherstraße 74
01307 Dresden
Phone: 0351 458 5222
Fax: 0351 458 4367
Email: Christoph.Roellig@uniklinikum-dresden.de

9 Assessment of Safety

9.1 Specification of Safety Parameters

9.1.1 Adverse Events

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Changes of laboratory parameters

- Intercurrent diseases and accidents
- Worsening of medical conditions/ diseases existing before inclusion into the trial
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.

If an AE shows an undulating course of intensity, it must be reported only once per cycle, indicating the highest CTCAE (Version 5.0) grade. If an event stops and later restarts within the same cycle, all occurrences must be reported.

A pre-existing disease or symptom is not considered an AE unless there is an untoward change in its intensity, frequency or quality. This change is documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

AEs are classified as "non-serious" or "serious".

The sponsor will keep detailed records of all adverse events reported by the investigators.

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the patient was at risk of death at the time of event and not to an event which hypothetically might have caused death if it had been more severe)
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity or
- Results in a congenital anomaly/ birth defect.
- Is medically significant (e.g. suspected transmission of an infectious agent via medicinal product). Moreover, there are other situations - such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

9.1.3 Protocol specific exemptions from SAE reporting

Myelosuppresion, thrombocytopenia, anemia and associated complications are expected events during leukema therapy. They are part of the treatment success and do not change the benefit-risk-assesment of the trial, except when prolonged myelosuppression is observed.

All leukemia-associated adverse events are to be reported on the adverse event pages of the eCRF, but, even if assessed as serious, leukemia-associated events, do not always require SAE-reporting as described in section 9.3.

If occurring from day 1-28 during intensive therapy (i.e. during induction, salvage and consolidation therapy) the following events do not require SAE-reporting:

- Anemia
- Leukopenia
- Neutropenia
- Thrombocytopenia
- Myelosuppresion (if not prolonged, specification see below)

Prolonged myelosuppression, i.e. pancytopenia with marrow hypocellularity continuing beyond day 28 or the start of a new therapy line (whichever comes first), has to be reported as an SAE if the investigator classifies the SAE as associated with the administration of one or both IMPs.

However, if occurring during maintentenace therapy or if the day of onset is after day 28 during induction, salvage or consolidation therapy all aforementioned adverse events require SAE-reporting as described in section 9.3.

9.1.4 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the applicable product information (Reference Safety Information (RSI)), e.g. Investigator's Brochure (IB), Summary of Product Characteristics (SmPC). Furthermore, reports which add significant information on specificity or severity of a known adverse reaction are counted as 'unexpected' events.

IMP	RSI
Glasdegib	IB
Gemtuzumab ozogamicin	SmPC

9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to IMP, and 'unexpected' for the respective IMP, i.e. the nature and/ or severity of which is not consistent with the applicable RSI are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent higher federal authority (i.e. BfArM), and to all participating investigators.

9.2 Period of Observation and Documentation

All AEs reported by the patient or detected by the investigator are collected during the trial, and must be documented on the appropriate forms of the eCRF. AEs must also be documented in the patient's medical records.

In this trial, all AEs that occur **from Day 1 of the 1st chemotherapy cycle** on are to be documented and, if applicable, reported as SAEs. The period of observation (safety follow-up) ends 8 weeks after the last administration of the IMP or placebo. All patients experiencing AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the outcome. The clinical course of the AE is followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition. This applies also to AEs ongoing at study end.

9.2.1 Grading of AEs

The grading of AEs in this trial is carried out on the basis of the 5-grade scale defined in the CTCAE (current version V5.0):

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE

A Semi-colon indicates 'or' within the description of the grades. A single dash (-) indicates a grade is not available.

*Activities of Daily Living (ADL) *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The grading of all AEs listed in the CTCAE is based on the information contained therein. The grading of all other AEs, i.e. those which are not listed in the CTCAE V5.0 are performed by a responsible investigator in accordance with the above criteria.

9.2.2 Relatedness between AEs and the IMP

The investigator evaluates each AE that occurred after administration of IMP regarding the causal relationship with the administration of the IMP, **background medication** (other chemotherapeutics), and the **underlying disease**. The evaluation of the IMP's relatedness to AEs is to be performed according to the following scale:

Y (Yes)	There is a reasonable possibility that the IMP caused the AE.
N (No)	There is no reasonable possibility that the IMP caused the AE (missing plausibility and/or clear alternative explanation).

9.2.3 Outcome of AEs

The outcome of an AE at the time of the last observation is classified as:

Recovered/ resolved	All signs and symptoms of an AE disappeared without any sequelae at the time of the last interrogation.
Recovering/ resolving	The intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution.
Not recovered/ not resolved	Signs and symptoms of an AE are mostly unchanged at the time of the last interrogation.
Recovered/ resolved with sequelae	Actual signs and symptoms of an AE disappeared but there are sequelae related to the AE.
Fatal	Resulting in death. If there are more than one AE only the adverse event leading to death (possibly related) is characterized as 'fatal'.
Unknown	The outcome is unknown or implausible and the information cannot be supplemented or verified.

9.2.4 Action taken with the IMP and Background Medication

The action taken with IMP or the background medication (BMed) is assigned to one of the following categories:

Dose not changed	No change in the dose of IMP / BMed.
Dose reduced	Reduction in the dose of IMP / BMed.
Temporary discontinuation	Temporary discontinuation of IMP / BMed.
Dose increased	Increase in the dose of IMP / BMed.
Drug withdrawn	Discontinuation of IMP / BMed.
Unknown	The information is unknown or implausible and it cannot be supplemented or verified.
Not applicable	The question is implausible (e.g., the patient is dead).

9.2.5 Countermeasures

The term 'Countermeasures' refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequelae. The following categories are used to categorize the countermeasures to adverse events:

None	No action taken
Drug treatment	Newly-prescribed medication or change in dose of a medication
Others	Other countermeasures, e.g. an operative procedure

9.3 Reporting of Serious Adverse Events by Investigator

All SAEs must be reported by the investigator to the KKS Heidelberg immediately without undue delay but not later than within 24 hours of obtaining knowledge using the "Serious Adverse Event" form. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event as well as an assessment of the relatedness between the event and the trial medication. Reporting is done by faxing a completed 'SAE Form' to the KKS Heidelberg.

Fax-number: + 49 (0)6221 56 33687

SAEs with a suspected causal relationship to one of the IMPs occurring to a patient after completion of the study should also be reported if the investigator becomes aware of them (although such information is not routinely to be sought or collected).

9.4 Expedited Reporting

SUSARs are to be reported to the ethics committee(s), regulatory authorities (i.e. BfArM) and to all participating investigators within regulatorily defined timelines, i.e. they are subject to an expedited reporting.

All SAEs are to be forwarded by e-mail immediately without undue delay but not later than within 24 hours of obtaining knowledge by the responsible person at KKS Heidelberg to the coordinating investigator or medical coordinator in order to perform a second assessment. The coordinating investigator or the joint coordinating investigator has to fill out a 'Second Assessment Form' for each SAE and return it by e-mail to the KKS Heidelberg within 48 hours.

E-mail: V-KKS.SAE@med.uni-heidelberg.de

The 'Second Assessment Form' contains the following information:

I) Assessment of relationship between SAE and IMP
II) Assessment of expectedness of SAE (derived from IB or SmPC)
III) Assessment of relationship between SAE and the underlying disease
IV) Statement if the benefit/ risk assessment for the trial did change as a result of SAE.

Expedited reporting is carried out by the KKS Heidelberg after unblinding of the respective patient's study treatment.

9.5 Pregnancy Reporting

9.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, study treatment has to be discontinued immediately. The outcome of any conception occurring from the date of the first dose until 3 month after the last dose should be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

If any pregnancy, suspected pregnancy, or positive pregnancy test occurs in the course of the study, it must immediately be reported to the KKS Heidelberg (acting on behalf of the sponsor) by fax using a 'Pregnancy Reporting Form'.

All pregnancies should be followed up and documented, even if the patient was withdrawn from the study, until their outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality). The outcome must be notified immediately by the investigator to the KKS Heidelberg (acting on behalf of the sponsor) within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy, which meets a seriousness criterion, the investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the KKS Heidelberg by fax within 24 hours of the investigator's knowledge of the event).

All neonatal deaths that occur within 30 days of birth should be reported as SAEs, without regard to causality. In addition, any infant death at any time thereafter that the investigator suspects as related to the exposure to the IMP should also be reported to the KKS Heidelberg by fax within 24 hours of the investigators' knowledge of the event.

The KKS Heidelberg (on behalf of sponsor) informs appropriately Pfizer representatives within one working day from the date the KKS, is aware of a pregnancy.

9.5.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and at least for 7 months following the last dose of GO and for at least 30 days following the last dose of glasdegib.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.

9.6 Reporting to the IMP Manufacturer

All SAEs, independently from any causal relationship provided by the investigator to the IMP, are to be reported by the KKS (the Sponsor's pharmacovigilance delegate) to Pfizer Pharma GmbH.

If not fatal or life-threatening SAEs are to be reported within 24 hours of the KKS' awareness of information meeting the minimum criteria for a valid report. Fatal or life-threatening SAEs are to be reported to Pfizer immediately at awareness irrespective of the extent of the available event information.

The date of awareness is to be clearly documented on the "Serious Adverse Event" form.

A detailed description of applicable reporting procedures and the addressee at Pfizer (email, Fax No.) is given in the safety manual of the study.

9.7 Emergency Unblinding

If it is medically imperative to know what trial medication the patient is receiving, the investigator or authorized medical staff should break the blind of the respective patient. The investigator or

the person who breaks the blind must record the date and the reasons for doing so in the online randomization tool (randomizer.at), the eCRF and in the patient's medical record. Whenever possible, the CI and/ or the sponsor should be contacted before the blind is broken.

The procedure of breaking the blind using randomizer.at is described in a separate document that is handed out prior to initiation of the respective clinical site.

9.8 Emergency Treatment

During and following a patient's participation in the trial, the investigator should ensure that adequate medical care is provided to a patient for any AE, including clinically significant laboratory findings. The investigator should inform a patient when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

10 Statistical Considerations

10.1 Research Hypothesis

This trial addresses two research questions:

1. Does GO-147 lead to an increased **MRD-negativity** rate as compared to GO-1?
2. Does high-dose cytarabine (HiDAC) + glasdegib lead to improved **event-free survival** as compared to HiDAC + placebo?

For the short-term endpoint (1) **MRD-negativity,** the hypotheses are as follows:

- $\mathbf{H_0^{ST}}$: there is no difference regarding the MRD-negativity rate for patients receiving GO-147 ($p_{GO\text{-}147}$) as compared to patients receiving GO-1 ($p_{GO\text{-}1}$) during induction therapy, i.e. $p_{GO\text{-}147} = p_{GO\text{-}1}$
- $\mathbf{H_1^{ST}}$: there is a difference regarding the MRD-negativity rate for patients receiving GO-147 as compared to the rate for patients receiving GO-1 during induction therapy, i.e. $p_{GO\text{-}147} \neq p_{GO\text{-}1}$

For the long-term endpoint (2) **event-free survival,** the hypotheses are as follows:

- $\mathbf{H_0^{LT}}$: there is no difference regarding event-free survival for patients receiving HiDAC + glasdegib as compared to patients receiving HiDAC + placebo during consolidation therapy
- $\mathbf{H_1^{LT}}$: there is a difference regarding event-free survival for patients receiving HiDAC + glasdegib as compared to patients receiving HiDAC + placebo during consolidation therapy

10.2 Analysis Variables

10.2.1 Primary Endpoints and Primary Estimands

For the gemtuzumab ozogamicin primary objective, the primary estimand according to the ICH-E9 (R1) [40] addendum is defined as:

Treatment: GO-147 (experimental arm) compared to GO-1 (control arm)

Population: all patients fulfilling the in- and exclusion criteria

Variable: MRD-negativity (MRD) defined as absence of leukemic cells at the end of the induction therapy assessed by flow-cytometry.

Post-randomisation events: if MRD-negativity cannot be measured, the outcome will be imputed (hypothetical strategy; see also Section 10.5.3), the outcome of patients who drop out of the study before MRD measurement will be imputed (hypothetical strategy; see also Section 10.5.3), changes in treatment, or discontinuation of treatment will be ignored (treatment policy strategy), any-cause death before MRD measurement will be regarded as MRD-positive (composite strategy).

Summary measure: Odds ratio for the endpoint MRD-negativity between the two treatment arms

For the glasdegib primary objective, the primary estimand is defined as:

Treatment: HiDAC + glasdegib (experimental arm) compared to HiDAC + placebo (control arm)

Population: all patients fulfilling the in- and exclusion criteria

Variable: Event-free survival (EFS) defined as the time from randomization to time until one of the following events, whichever occurs first: a) failure to obtain complete remission (CR) or complete remission with incomplete hematological recovery (CRi), b) relapse from CR/CRi for patients with induction success or c) death from any cause.

Post-randomisation events: death from any cause is incorporated into the variable definition (composite strategy); changes in treatment and termination of treatment will be ignored (treatment policy strategy); event-free patients at the end of the follow-up period will be censored and patients who were lost to follow up or dropped out of the trial will be censored at the last observation (hypothetical strategy).

Summary measure: Hazard ratio for the endpoint disease-free survival between the two treatment arms

10.2.2 Secondary Endpoints

- **Complete remission rate (CRR)**, defined as the proportion of patients experiencing CR/CRi after induction therapy

- **Relapse-free survival (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. Patients without an applicable event are censored on the last date of follow-up. [time frame: up to LPLV]

- **Overall survival (OS)**, defined as the time from randomization to time of death from any cause. Patients without an applicable event are censored on the last date of follow-up. [time frame: up to LPLV]

- **Patient-Reported Outcomes including Quality of Life:**

    - **Health-related quality of life (QoL)** is calculated as the new EORTC QLQ-C30 Summary Score recommended by the EORTC Quality of Life Group, which has been recently developed and evaluated [41]. In addition, the EORTC QLQ function and symptom scores is calculated according to the actual EORTC Scoring Manual [42].

    - **Fatigue** is calculated from the EORTC QLQ-FA12 according to the EORTC Scoring Manual [42].

    - **Sleep problems** is calculated from the PSQI according to the corresponding scoring guidelines [43].

    - **Perceived cognitive impairments** and **impact of cognitive changes** is calculated from the FACT-cog according to the corresponding scoring manual.

    - **Anxiety** is calculated from the PHQ-4 according to the corresponding scoring manual [44].

    - **Depression** is calculated from the PHQ-4 according to the corresponding scoring manual [44].

    - Health state utilities are calculated based on the SF-36 generic instrument [45].

- **Effectiveness** of the investigational treatment is measured using the SF-36 generic instrument. A preference based single index is calculated using the SF-6D measure that facilitates obtaining health utilities and quality adjusted life years (QALYs).
- **Health care resource utilization** and costs are measured through the treatment course. Resource units and unit costs are collected separately by self-administered questionnaires at the end of each cycle and 3-monthly during maintenance therapy, as well as using relevant data from the eCRF and German reimbursement database.

10.3 Sample Size Calculation

The trial incorporates two primary endpoints, namely the short-term endpoint **MRD-negativity (MRD)** and the long-term endpoint **event-free survival (EFS).**

The short-term evaluation involves a comparison of MRD-negativity rates between the experimental arm GO-147 and the control arm GO-1. The null hypothesis is $\mathbf{H_0^{ST}}$: $p_{GO\text{-}147} = p_{GO\text{-}1}$. Assuming an overall MRD-negativity rate of $p_{GO\text{-}147}$=0.315 for the GO-147 arm and overall MRD-negativity rate of $p_{GO\text{-}1}$=0.14 (corresponding to an odds ratio of OR=(0.315*(1-0.14)/((1-0.315)*0.14)=2.8248, see details on determination of MRD-negativity rates in Sections 10.3.2 and 10.3.4) for the GO-1 arm, as well as a 3% dropout rate, a total number of 252 evaluable patients are needed to reject the null hypothesis at a two-sided significance level of 2.5% with a power of approximately 85% using a chi-squared test (details of the calculation are provided in Sections 10.3.2 and 10.3.4). It is assumed that using a generalized linear mixed model adjusting for center, age and ECOG PS yields an increased power due to part of the variance being explained by confounders.

The long-term evaluation involves a two group comparison of EFS between the experimental arm HiDAC + glasdegib and the control arm HiDAC + placebo. The null hypothesis is $\mathbf{H_0^{LT}}$: There is no difference in EFS between the HiDAC + glasdegib arm as compared to the HiDAC + placebo arm. Assuming an EFS event proportion at 2 years of 44% for the experimental arm and an EFS event proportion at 2 years of 65% for the control arm (corresponding to a hazard ratio of θ=log(1-0.44)/log(1-0.65)=0.552, see details on determination of 2-year EFS rates in Sections 10.3.3 and 10.3.4), as well as a 5% dropout rate, a total number of d=122 events and 186 evaluable patients are needed to reject the null hypothesis at a significance level of 2.5% with a power of approximately 85% (details of the calculation are provided in Sections 10.3.3 and 10.3.4). When assuming a slightly higher EFS event proportion at 2 years of 47.5% still corresponding to a clinically meaningful treatment effect of θ=log(1-0.475)/log(1-0.65)=0.614, a power of 80% will still be achieved with the planned sample size of 252 patients (see Table 5 in Section 10.3.4). As for the short-term endpoint, it is assumed that using a Cox regression model adjusting for center, age and ECOG PS (0 / >0) yields an increased power due to part of the variance being explained by confounders. Calculations were performed using the software R 4.1.0 with the package rpact 3.1.0.

10.3.1 General Considerations and Test Hypotheses

In the following, we illustrate the considerations on the choice of the sample size for the research questions GO-147 vs. GO-1 and HiDAC + glasdegib vs. HiDAC + placebo within a 2x2 factorial design. The two research questions result in four treatment arms:

A) GO-147 & HiDAC + glasdegib
B) GO-1 & HiDAC + glasdegib
C) GO-147 & HiDAC + placebo
D) GO-1 & HiDAC + placebo

The trial incorporates two primary endpoints, namely **MRD-negativity (yes/no)** defined as absence of leukemic cells at the end of the induction therapy

and **event-free survival (EFS)** defined as the time from randomization until one of the following events occurs first:

(i) failure to obtain CR or CRi,
(ii) relapse from CR/CRi or
(iii) death.

Within this trial, it is hypothesized that GO-147 leads to an increased MRD-negativity rate as compared to GO-1, and that HiDAC + glasdegib leads to an improved EFS as compared to HiDAC + placebo. It is assumed that there is no (relevant) treatment interaction.

The assessment of the two null hypotheses $\mathbf{H_0^{ST}}$ for the short-term endpoint MRD-negativity and $\mathbf{H_0^{LT}}$ for the long-term endpoint EFS requires an adjustment of the (two-sided) local significance levels α_{ST} and α_{LT} in order to control the family-wise error rate in the strong sense at a global two-sided significance level of α=0.05. Therefore, the Bonferroni-Holm approach [46] (Holm 1979) is used, being uniformly more powerful than the Bonferroni approach without requiring any additional assumptions.

10.3.2 Considerations for the Short-Term Endpoint MRD-Negativity

The proportion of patients who achieve a complete remission (CR/CRi) of acute myeloid leukemia (AML) after treatment is assumed to be 70% irrespective of the treatment group [14]. For a patient from one of the GO-1 groups B/D with a CR/CRi, the probability to be MRD-negative is assumed to be 20% [19]. Hence, the overall MRD-negative rate for patients from one of the two GO-1 groups is assumed to be

$$p_{GO\text{-}1}=0.7 \times 0.2=0.14.$$

Regarding the MRD-negativity rate in the GO-147 patients with a CR/CRi, 4 different scenarios were assumed during the planning phase, namely 50%, 45%, 40% and 35%. Accordingly, the MRD-negativity rate is assumed to be either

- $p_{GO\text{-}147}=0.7 \times 0.5 = 0.35$,
- $p_{GO\text{-}147}=0.7 \times 0.45 = 0.315$,
- $p_{GO\text{-}147}=0.7 \times 0.4 = 0.28$ or
- $p_{GO\text{-}147}=0.7 \times 0.35 = 0.245$

The dropout rate for the assessment of the short-term endpoint is assumed to be 3%.

10.3.3 Considerations for the Long-Term Endpoint EFS

Since the proportion of patients who achieve a CR or CRi of acute myeloid leukemia (AML) after treatment is assumed to be 70% irrespective of the treatment group, 30% of all patients experience the event “failure to obtain CR or CRi” regardless of the treatment. For those patients from the “HiDAC only” arms C and D with a CR or CRi, it is assumed that a proportion of 65% either relapse or die two years after randomization. Hence, the proportion of patients from arms C and D with an event after two years, π_{HiDAC}, amounts to

$$\pi_{HiDAC} = 0.3 +(0.7 \times 0.5)=0.3+0.35=0.65.$$

Regarding the proportion of patients from the glasdegib groups A and B who either experience a relapse or die within two years after randomization but have achieved a complete remission before, 4 different scenarios were assumed during the planning phase of the trial, namely 20%, 25%, 30%, 35% and 40%. Accordingly, the following scenarios for the event rate $\pi_{HiDAC+GD}$ after two years are considered:

- $\pi_{HiDAC+GD} =0.3 + (0.7 \times 0.2) = 0.3 + 0.14=0.44$
- $\pi_{HiDAC+GD} =0.3 + (0.7 \times 0.25) = 0.3 + 0.175=0.475$
- $\pi_{HiDAC+GD} =0.3 + (0.7 \times 0.3) = 0.3 + 0.21=0.51$
- $\pi_{HiDAC+GD} =0.3 + (0.7 \times 0.35) = 0.3 + 0.245=0.545$
- $\pi_{HiDAC+GD} =0.3 + (0.7 \times 0.4) = 0.3 +0.28 =0.58$

A dropout rate of 3% is expected for the assessment of the short-term endpoint, which is induced by a proportion of patients for which a MRD measurement cannot be conducted due to a lack of a leukemia-associated phenotype. For the long-term endpoint EFS, a dropout rate of 5% is expected 2 years after randomization and dropout times are assumed to be exponentially distributed. The two distinct dropout probabilities are assumed to be uncorrelated.

Furthermore, the assumed accrual time amounts to 24 months, and the follow-up time is assumed to be 24 months as well.

10.3.4 Required Sample Sizes

In the following, the required total sample sizes are displayed for the assessments of the short- and long-term endpoint. The required sample sizes are based on the assumptions in the previous Sections. For the comparison of the short-term endpoint, MRD-negativity, the sample size calculation is based on the comparison by the chi-squared test, while for the comparison of the long-term endpoint, EFS, the log-rank test is applied with the sample size formula by Schoenfeld [47]. Sample sizes were determined for a power of 1-β=0.8, 0.85, and 0.9, respectively. The required total sample sizes for the Bonferroni approach are presented in Table 5.

Table 5: Total sample sizes for Bonferroni approach

	1-β=0.8	**1-β=0.85**	**1-β=0.9**
$p_{GO\text{-}147}$ = 0.7 x 0.5 = 0.35	164	184	212
$p_{GO\text{-}147}$ = 0.7 x 0.45 = 0.315	224	**252**	292
$p_{GO\text{-}147}$ = 0.7 x 0.4 = 0.28	332	376	432
$p_{GO\text{-}147}$ = 0.7 x 0.35 = 0.245	552	624	720
$\pi_{HiDAC+GD}$ = 0.3 + (0.7 x 0.2) = 0.44	164	**186**	214
$\pi_{HiDAC+GD}$ = 0.3 + (0.7 x 0.25) = 0.475	236	268	308
$\pi_{HiDAC+GD}$ = 0.3 + (0.7 x 0.3) = 0.51	368	414	480
$\pi_{HiDAC+GD}$ = 0.3 + (0.7 x 0.35) = 0.545	646	730	844
$\pi_{HiDAC+GD}$ = 0.3 + (0.7 x 0.4) = 0.58	1434	1620	1872

Assumptions: $p_{GO\text{-}1}$=0.14, π_{HiDAC}=0.65, α_{ST}= α_{LT}=0.025. Dropout rates of 3% for the short-term endpoint and 5% for the long-term endpoint are already incorporated.

Based on the Bonferroni approach with an aspired power of 1-β=0.85 for both hypotheses, and assuming that $p_{GO\text{-}147}$=0.315 and $p_{GO\text{-}1}$=0.14 (corresponding to an assumed odds ratio of OR=2.8248) , while $\pi_{HiDAC+GD}$=0.44 and π_{HiDAC} =0.65 (corresponding to an assumed hazard ratio of θ=0.552), a total sample size of N=max(252, 186)=252 patients needs to be randomized. Using the Bonferroni-Holm approach to control for multiple testing yields a further increase in power.

10.4 Analysis Populations

10.4.1 Full Analysis Population

The Full Analysis Population includes all randomized patients with treatment groups assigned in accordance with the randomization, regardless of the treatment actually received. The analysis of data using the Full Analysis Population therefore follows the principles of Intention To Treat (ITT). This will be the primary analysis population for the primary and secondary efficacy endpoints.

If there are patients who were randomized but did not subsequently receive treatment, these are excluded from the Full Analysis Population for sensitivity analysis as they provide no information about efficacy or safety of the interventions under investigation. Then the analysis follows the modified ITT (m-ITT) principle [48].

10.4.2 Per Protocol Population

The Per Protocol (PP) Population comprises all patients of the Full Analysis Population without major protocol deviations. Definition of major protocol deviations is given in the statistical analysis plan (SAP). Analyses based on the PP Population serve as sensitivity analyses in order to assess the robustness of the results obtained from the Full Analysis Population.

10.4.3 Safety Population

The Safety Population is the primary population for the evaluation of treatment administration/compliance and 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.

10.5 Statistical Methods

10.5.1 General Considerations

The statistical evaluation is carried out under the supervision of the Supervising Statistician. Statistical analysis is based on the International Conference on Harmonization (ICH) Guidelines “Structure and Content of Clinical Study Reports” (ICH E3) and “Statistical Principles for Clinical Trials” (ICH E9). All statistical procedures are done according to the current Standard Operating Procedures (SOPs) of the Institute of Medical Biometry and Informatics, University of Heidelberg (IMBI).
All data recorded in the eCRF describing the sample, the efficacy and the safety are analyzed descriptively. Categorical data are presented in contingency tables with frequencies and percentages. Continuous data are summarized with at least the following: sample size, median, quartiles, mean, standard deviation, minimum and maximum.
The detailed methodology for the statistical analysis is described in the statistical analysis plan (SAP), which is finalized before recruitment starts. Statistical analysis is performed using SAS v9.4 or higher.

10.5.2 Demographic and other Baseline Characteristics

Descriptive statistics are performed for all demographic data and baseline characteristics.

10.5.3 Analysis of the Primary Endpoints

Since hypothesis tests are performed for both the short-term endpoint MRD-negativity and the long-term endpoint EFS, the null hypotheses H_0^{ST} and H_0^{LT} are tested using the Bonferroni-Holm approach in order to control the family-wise error rate in the strong sense. Hence, the smaller of the short-term and long-term p-values p^{ST} and p^{LT} are tested at a two-sided significance level of $\alpha=0.025$. In case the null hypothesis corresponding to the smaller p-value is rejected, the remaining null hypothesis corresponding to the larger p-value is tested at a two-sided significance level of $\alpha=0.05$. In case the null hypothesis corresponding to the smaller p-value cannot be rejected, then the null hypothesis corresponding to the larger p-value has to be accepted as well.

The short-term primary endpoint MRD-negativity is analyzed using a generalized linear mixed model with the binary dependent variable “Patient MRD-negative (yes/no)”, including the fixed factors induction therapy (GO-147 vs. GO-1), ECOG PS (0 vs. 1-2), age (in years), sex, and the random factor “center”, using a variance components covariance matrix and residual log pseudo-likelihood as minimization criterion to fit the model. Due to the expected few number of patients and events per center, we chose to include “center” as a random factor in order to ensure stability for the statistical model based on the recommendation of Kahan & Harhay [49]. The short-term endpoint null hypothesis $\mathbf{H_0^{ST}}$ is tested based on the odds ratio of the factor induction therapy (GO-147 vs. GO-1). Missing values for the short-term primary endpoint MRD-negativity are replaced using multiple imputation by using of the fully conditional specification method [50],

taking the variables, treatment group, age and ECOG PS into account. A complete-case analysis is done as a sensitivity analysis. Odds ratios are reported alongside with 97.5% and 95% confidence intervals, and a possible center effect is assessed by calculating the intra-class correlation coefficient and by presenting the results stratified for center.

The long-term primary endpoint EFS is analyzed using a Cox regression frailty model with the dependent variable EFS, including the fixed factors maintenance therapy (HiDAC+ glasdegib vs. HiDAC), induction therapy (GO-147 vs. GO-1), ECOG PS (0 vs. 1-2), age (in years), sex, and the random factor "center". Analogously to the short-term endpoint, a random-intercept model adjusting for "center" is used due to the expected few number of events per center. The long-term endpoint null hypothesis $\mathbf{H_0^{LT}}$ are tested by using the adjusted-degrees of freedom approach for frailty models proposed by Gray [51] which is implemented in the SAS procedure PHREG. Dropout and loss-to-follow-up are treated as censoring events. Hazard ratios are reported alongside with 97.5% and 95% confidence intervals, and a possible center effect is assessed by calculating the intra-class correlation coefficient. EFS probabilities over time are displayed using survival estimates calculated using the Kaplan-Meier method.

Sensitivity analyses of the primary endpoints incorporate an analysis within the PP Population. Furthermore, the treatment effects are assessed descriptively within several subgroups of interest to identify potential prognostic and predictive factors. A sensitivity analysis of the long-term primary endpoint additionally includes the interaction between maintenance therapy and induction therapy. A further sensitivity analysis includes the fixed factor "switch to "SOC^{PhC}" and the interaction between maintenance therapy and "switch to "SOC^{PhC}".

10.5.4 Analysis of the Secondary Endpoints

Secondary time-to event endpoints are analyzed analogously to the primary short-term endpoint EFS by using cox regression frailty models adjusting for treatment, age, ECOG PS and center, determining hazard ratios with 95% confidence intervals and (descriptive) p-values. Furthermore, event probabilities over time are displayed using survival estimates calculated using the Kaplan-Meier method. The secondary endpoint complete remission rate (CRR) is analyzed analogously to the primary short-term endpoint, using generalized linear mixed models to estimate odds ratios with corresponding 95% confidence intervals and descriptive p-values.

Safety Analysis

The assessment of safety is based mainly on the frequency of adverse events (see Section 9) and on the number of laboratory values that fall outside of pre-determined ranges and/or show prominent worsening from baseline during the study phase. Adverse events are summarized by presenting the number and percentage of patients having any adverse events or serious adverse events, and having each individual type of adverse event, and by determining and summarizing the maximum individual toxicity grade (over all forms of toxicity) for each treatment cycle during the study phase. Furthermore, the most common AEs (those occurring in at least 10% of the treatment group) are determined. Any other information collected (e.g. severity or relatedness to study drug) are summarized as appropriate. Laboratory data are summarized by presenting summary statistics of raw data and changes from baseline values. Incidence rates are summarized along with two-sided Pearson-Clopper 95% confidence intervals and analyzed by (descriptive) chi-squared tests.

Patient-Reported Outcomes (PROs) including Quality of Life Analysis (QoL)

The QoL scales are scored and analyzed according to the EORTC recommendations as described in the EORTC QLQ-C30 scoring manual [52]. The Quality of Life subscales and single item sub-scores are summarized by the mean, standard deviation and median and plotted over time for all four treatment groups. The change from baseline in QoL until a respective time point is examined by means of a general linear mixed model adjusting for treatment group, ECOG PS

(0 vs. 1-2), age (in years) and sex as fixed factors and center as random factor, calculating least square means estimates and 95% confidence intervals. For details on analysis of patient-reported outcomes (PROs) see Section 10.2.2.

With regard to the analysis of data from SF-36 questionnaire see below (Health Economic Analysis).

Health Economic Analysis

Effectiveness of the investigational treatment is measured using the SF-36 instrument. Dimension scores and summary scores for physical and mental health are obtained and analyzed according to the SF-36 scoring manual [45] and summarized over time by mean, standard deviation and median for separate treatment arms. A preference based single index is calculated using the SF-6D measure that facilitates obtaining health utilities for the use of cost-effectiveness analysis [53]. Health care resource utilization data is summarized by mean, standard deviation and median for separate treatment arms. To calculate total costs, micro-costing approach is intended to be used. Health care resource utilization units are multiplied by German standard unit costs of the relevant resource items by patient.

Various clinical trial data are used to conceptualize and populate the cost-effectiveness model. QALYs are calculated according to state of the art health economic methodology using Kaplan-Meier curves of OS and RFS to determine the expected length of life and SF-36 scores to provide health state utilities (i.e. quality of life information) in the model. To extrapolate the data over the model time horizon, survival curves are fitted by treatment arms to OS and RFS data and the base case curve is selected on the basis of goodness of fit, if data quality permits. Health state utilities mapped from the EORTC QLQ-C30 instrument are used in scenario analysis. Frequency and severity of AEs are used to calculate AE treatment costs and disutilities. Health care resource utilization units and unit costs are used to calculate the expected cost through the patients´ treatment course, including medical costs, disease monitoring, hospitalizations, and potential other health care resources. Non-parametric, empirical distribution functions are built into the cost-effectiveness model to assess uncertainty around the model estimates, if data quality permits.

Furthermore, a mapping function between EORTC QLQ-C30 and SF-36 is generated and validated.

10.5.5 Patients' Disposition and other Analyses

- Patients' disposition and reasons for ending the study are presented in frequency distribution tables and individual data listing.
- Individual data are presented in listings.

10.5.6 Multiple Comparisons/ Multiplicity

Multiple testing concerning the primary endpoints is accounted for using the Bonferroni-Holm method. For secondary endpoints, no formal hypothesis testing is done, and p-values are solely to be interpreted descriptively. Thus no additional adjustment for multiple testing is performed.

10.5.7 Handling of Missing Data

Missing values for the short-term endpoint MRD-negativity are replaced using multiple imputation (see Section 10.5.3 for details). For patients with incomplete follow-up, time to last follow-up date is used as the censoring time in the analysis of time-to-event data. Otherwise, no imputation of missing data is conducted.

11 Data Management

11.1 Data Collection

The data collection is performed using an eCRF. Data collection using the eCRF can only be done by authorized persons. All study data are password-protected. The eCRF provides several checks for completeness and consistency. Each entry or change of data is tracked with name and exact date (audit trail). When data has been entered, reviewed, edited and Source Data Verification (SDV) performed, the investigator is notified to sign the eCRF electronically as per agreed project process, and data is locked to prevent further editing. A copy of the eCRF is to be archived at the study site.

All data collected as stipulated by the study protocol including clinical and laboratory data (with regard to documentation of safety laboratory data see sections 7.4.1 and 0) is documented by the investigator or an authorized member of the study team in the patient's medical record and in the eCRF. The investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified by source data. The eCRF has to be filled out according to the specified eCRF Completion Guidelines.

PRO questionnaires are paper-based, are completed by patients and serve as source data. Upon completion questionnaires (apart from SF-36, see below) are returned (e.g. mailed back or collected by the monitor) to central unit for Quality of Life & Patient-Reported Outcomes (see page 2 “Responsibilities”). The questionnaires are then recorded using the TELEFORM® system (Cardiff) and undergo a computer assisted manual verification. Derived data sets, combining eCRF and PRO data are produced at time points of analyses. The link between the questionnaires and the eCRF is maintained by a combination of a unique number for each questionnaire and the patient-ID (PA T-ID) which is recorded in the eCRF.

Health care resource utilization questionnaires and the SF-36 questionnaire are paper-based and self-administered by the patients. Upon completion, the questionnaires are returned (e.g. mailed back or collected by the monitor) to the Division of Health Economics. The questionnaires are recorded electronically and validated by a second person to ensure accuracy in the data capturing. Derived data sets are merged with relevant queries from the eCRF. The link between the health economic questionnaires and the eCRF is maintained by a combination of a unique number for each questionnaire and the patient-ID (PAT-ID) which is recorded in the eCRF.

11.2 Data Handling

Data entries undergo an automated check for plausibility and consistency. In case of implausibility, 'warnings' are produced. A responsible investigator is obliged either to correct the implausible data or to confirm its authenticity and to give an appropriate explanation. If not corrected, the data are flagged, enabling a convenient check of all questionable entries. The responsible monitor checks all flagged data and generates questions (“queries”) that are sent back to the responsible investigator. The investigator has to resolve all 'discrepancies'.

Further checks for plausibility, consistency, and completeness of data are performed during and after completion of the study. Queries are generated on the basis of these checks, combined with a visual control by a responsible monitor/data manager.

All missing data or inconsistencies are reported back to the sites and clarified by the responsible investigator. If no further corrections are to be made in the trial database it is declared closed and used for statistical analysis.

All data management activities are done according to the current Standard Operating Procedures (SOPs).

11.3 Storage and Archiving of Data

According to legal obligations (§13 of the German GCP-Regulation) all important documents (e.g. CRFs) collected within the scope of this trial are to be archived for at least 10 years after its

termination. The trial documents will be destroyed within one and a half year after the end of this retention period.

The investigator(s) archive all trial data (source data and Investigator Site File (ISF) including Patient Identification List and relevant correspondence) according to the Section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations. The Patient Identification List is archived for at least 15 years after trial termination.

If the investigator relocates, retires, or for any reason withdraws from the study, the NCT Trial Center should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the NCT Trial Center. The investigator must obtain CIs written permission before disposing of any records, even if archiving requirements have been met.

12 Ethical and Legal Aspects

12.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the current version of the Declaration of Helsinki. The trial is carried out in keeping with local legal and regulatory requirements.

12.2 Patient Information and Informed Consent

Before being admitted to the clinical trial, the patient must consent in written form to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The originally personally signed and dated Informed Consent Form must be kept on file by the investigator(s), and the execution of the signature must be documented in the case report form.

A copy of the signed informed consent document must be given to the patient. The documents must be in a language easily understandable to the patient and must clearly state who informed the patient, which is confirmed by the dated signature of the responsible investigator

If new safety information results in significant changes in the risk/benefit assessment, or if changes are made in the protocol, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) must be informed of the new information and must give their written informed consent to continue the study.

12.3 Confidentiality

The data obtained in the course of the trial are treated pursuant to the General Data Protection Regulation (EU-DSGVO, EU 2016/679) and the Data Protection Law of the Federal State (Landesdatenschutzgesetz), and the § 40 (2a) AMG.

During the clinical trial, patients are identified solely by means of an individual identification code (Patient ID). Storage of trial findings on a computer is done in accordance with local data protection law and handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation are fulfilled in its entirety.

The patient consents in writing to relieve the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons may inspect the patient-related data collected during the trial, ensuring the data protection law.

The investigator has to maintain a patient identification list (Patient IDs with the corresponding patient names) to enable records to be identified.

Patients who did not consent to circulate their pseudonymized data must not be included into the trial.

12.4 Responsibilities of Investigator

The Coordinating Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol and any amendments, the trial treatments, and their trial-related duties and functions.

The Coordinating Investigator should maintain a list of investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties (Log of Staff).

The investigators should support monitoring, auditing and inspections.

12.5 Approval of Trial Protocol and Amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents are submitted to the independent Ethics Committee (EC) as well as to the competent federal authority (BfArM). A written favorable vote of the EC and an (implicit) approval by the competent higher federal authority are a prerequisite for initiation of the clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first patient is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes (see §10, (1) of German GCP-Regulation) are to be submitted to EC and the competent federal authority in writing as amendments. They have to be approved by the EC and the competent federal authority.

The Coordinating Investigator or the NCT Trial Center, and if applicable the investigator(s) are keeping a record of all communication with the EC and the regulatory authorities.

12.6 Continuous Information to Independent Ethics Committee

Pursuant to the German Drug Law (AMG) and the GCP Regulation, the EC and the competent higher federal authority are informed of all suspected unexpected serious unexpected adverse reactions (SUSARs) and all AEs resulting in death or being live-threatening, which occur during the trial. Both institutions are informed in case the benefit-risk assessment did change or any other new and significant hazards for patients' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) is submitted once a year (Development Safety Update Report (DSUR)).

The EC and the regulatory authorities must be informed of the end of the trial. They have to be provided with a summary of trial results within one year after the end of the clinical phase (LPLV).

12.7 Notification of Regulatory Authorities

The local regulatory authorities as responsible for each particular investigator and the competent higher federal authority are informed before the beginning, during and at the end of the trial according to §67 AMG and §13 GCP-V. NCT Trial Center is obliged to notify his/ her local regulatory authority and the competent higher federal authority according §67 AMG and §12 (1, 2, 6) GCP-V.

12.8 Registration of the Trial

Prior to the beginning of the clinical phase (FPFV) the coordinating investigator registers the trial at a public accessible clinical trial register having the status of a primary register according to the International Clinical Trials Registry Platform (ICTRP) and correspondingly is listed at the International Clinical Trials Registry Platform of the World Health Organization (WHO,

http://www.who.int/ictrp/en/). The requirements are fulfilled by the European Clinical Trials Register and submission of EMA Module 1 (Clinical Trial Application Form).

12.9 Insurance

According to § 40 AMG, the sponsor subscribes to an insurance policy which covers in its terms and provisions its legal liability for injuries caused to participating persons. The insurance policy also covers any damage done to the patient, even if the harm done arises out of strictly following the procedures described in this protocol and abiding as applicable law and professional standards. The insurance was taken out at HDI Global SE (insurance number: 57 010310 03018/03152, maximum limit: € 500.000 per participating person).

Any impairment of health which might have occurred in consequence of trial participation, and is as such assumed to be an insurance case, must be notified to the insurance company. The patient is responsible for notification. The insured person must agree to help clarifying the cause and the extent of damage with all appropriate measures. He is also obliged to take measures by himself to reduce damage as much as possible. During the conduct of the trial, the patient must not undergo other clinical treatment without having consulted the investigator except for cases of emergency. The patient is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance must be delivered to the patient.

The insurance company has to be informed about all amendments that could affect patients' safety, and must also receive the actual version of the informed consent.

12.10 Biological Samples

Within the scope of this study biological samples (see Sections 7.3 and 7.4) are stored to develop further knowledge and understanding of diagnostic, prognostic and predictive markers present in AML patients, including their potential association with the study treatment (see section 2.3). Pseudonymization of all samples is done in a two-step procedure, directly at sampling and when datasets are stored. Applicable data are to be archived for at least 10 years after termination of the study (details see Section 11.3).

Responsibilities for storage of biological samples lie with the central molecular genetics laboratory of the University Hospital Heidelberg (responsible persons and address given on page 3). Data ownership is and will remain with the University Hospital Heidelberg.

On the occasion of the informed consent procedure patients are explicitly informed about the arrangements for sample storage including their right to withdraw consent for futher use of their biosamples at any time and that samples will be disposed in this case.

13 Quality Assurance

13.1 Monitoring

Monitoring is done by personal visits from a clinical monitor and by centralized monitoring according to the monitoring plan. The investigator must allow the monitor to verify all essential documents and must provide support at all times to the monitor. Monitoring is done in a risk-based manner.

By frequent communications (e-mails, letters, telephone, fax), the site monitor and the central monitor ensure that the trial is conducted according to the protocol and to regulatory requirements.

13.2 Inspections / Audits

Regulatory authorities and auditors authorized by the sponsor may request access to all source documents, the CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14 Agreements

14.1 Financing of the Trial

The trial is be co-financed by funds of the German Research Organization (DFG- SCHL 2118/2-1). The study is supported by Pfizer Pharma GmbH. Study drug is provided free-of-charge by Pfizer Pharma GmbH.

The funding organizations did not influence the study design nor will they influence the results of this trial.

14.2 Declaration of Interests

Before the start of the trial, the investigators disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsors/ a funding company, in the investigational product(s), or any commercial organization being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

14.3 Dissemination Policy

14.3.1 Access to data

After publication of the complete trial access to selected raw data is intended according to the applicable process [54].

14.3.2 Reports

The biostatistician prepares the final trial report together with the Coordinating Investigator within 12 months after the end of the study (database lock).

Interim safety reports (DSURs) are prepared by the pharmacovigilance officer together with the Coordinating Investigator in accordance with legally required timeframes; data reconciliation is carried out where necessary and possible together with the data management based on already available CRF-AE data.

14.3.3 Publication

All information concerning the trial is confidential before publication.

Trial results will be published in peer-reviewed medical journals.

15 Signatures

The present trial protocol was subject to critical review and has been approved in the present version by the person undersigned. The information contained is consistent with:

- The current benefit-risk assessment of the investigational medicinal product
- Moral, ethical, and scientific principles governing clinical research as set out in the principles of GCP and in the applicable version of Declaration of Helsinki.

The investigators will be supplied with details of any significant or new finding, including relevant safety information relating to treatment with the investigational medicinal product.

Date: 21.12.2021 Signature: 

_____ _____

Prof. Dr. Richard F. Schlenk

Function: Coordinating Investigator (LKP) according to § 40 German Drug Law (AMG) and sponsor representative

16 Declaration of Investigator(s)

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enroll the first patient only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all patients before enrolment.

I know the requirements for accurate reporting of serious adverse events, and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described.

I agree that my personal data in the role as investigator as well as the data of the study site may be published and/or submitted to the local authorities and/or ethical committees and/or registries in order to adequately report this clinical trial in accordance with the respective laws and regulations (e.g. §42b & §67 AMG, §12.1 GCP-V and DSGVO).

Trial Center

Date	Name (Investigator):	Signature:

Date	Name (Deputy):	Signature:

Please return this page with all signatures to the following recipients:

Project Management: by email to GnG@nct-heidelberg.de or by fax to 0221 56-5863

Monitoring: by email to your respective monitor

- Maret.Orlik@med.uni-heidelberg.de or
- Friederike.Dominick@med.uni-heidelberg.de or
- Wiebke.Wagner@med.uni-heidelberg.de

or by fax to 06221 56-33508

18 References

[1] Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. N. Engl. J. Med. 2015;373(12):1136–52.

[2] Dombret H, Gardin C. An update of current treatments for adult acute myeloid leukemia. Blood 2016;127(1):53–61.

[3] Schlenk RF, Döhner H. Genomic applications in the clinic: use in treatment paradigm of acute myeloid leukemia. Hematol. Am Soc Hematol Educ Progr. 2013;2013(1):324–330.

[4] Döhner H, Estey E, Grimwade D, *et al.* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424–447.

[5] Nagel G, Weber D, Fromm E, *et al.* Epidemiological, genetic, and clinical characterization by age of newly diagnosed acute myeloid leukemia based on an academic population-based registry study (AMLSG BiO). Ann. Hematol. 2017;96(12):1993–2003.

[6] Schlenk RF. Post-remission therapy for acute myeloid leukemia. Haematologica 2014;99(11):1663–70.

[7] Papaemmanuil E, Gerstung M, Bullinger L, *et al.* Genomic Classification and Prognosis in Acute Myeloid Leukemia. N. Engl. J. Med. 2016;374(23):2209–2221.

[8] Gerstung M, Papaemmanuil E, Martincorena I, *et al.* Precision oncology for acute myeloid leukemia using a knowledge bank approach. Nat. Genet. 2017;49(3):332–340.

[9] Arber DA, Orazi A, Hasserjian R, *et al.* The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391–2405.

[10] Larson RA, Boogaerts M, Estey E, *et al.* Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). Leukemia 2002;16(9):1627–1636.

[11] Petersdorf SH, Kopecky KJ, Slovak M, *et al.* A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood 2013;121(24):4854–60.

[12] Delaunay J, Recher C, Pigneux A, *et al.* Addition of gemtuzumab ozogamycin to chemotherapy improves event-free survival but not overall survival of AML patients with intermediate cytogenetics not eligible for allogeneic transplantation. Results of the GOELAMS AML 2006 IR Study. Blood 2011;118(21):79.

[13] Burnett AK, Hills RK, Milligan D, *et al.* Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J. Clin. Oncol. 2011;29(4):369–77.

[14] Castaigne S, Pautas C, Terré C, *et al.* Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet (London, England) 2012;379(9825):1508–16.

[15] Burnett AK, Russell NH, Hills RK, *et al.* Addition of Gemtuzumab Ozogamicin to Induction Chemotherapy Improves Survival in Older Patients With Acute Myeloid Leukemia. J. Clin. Oncol. 2012;30(32):3924–3931.

[16] Lambert J, Pautas C, Terré C, *et al.* Gemtuzumab ozogamicin for *de novo* acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. Haematologica 2019;104(1):113–119.

[17] Hills RK, Castaigne S, Appelbaum FR, *et al.* Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet. Oncol. 2014;15(9):986–96.

[18] Burnett A, Cavenagh J, Russell N, *et al.* Defining the dose of gemtuzumab ozogamicin in combination with induction chemotherapy in acute myeloid leukemia: a comparison of 3 mg/m2 with 6 mg/m2 in the NCRI AML17 Trial. Haematologica 2016;101(6):724–731.

[19] Lambert J, Lambert J, Nibourel O, *et al.* MRD assessed by WT1 and NPM1 transcript levels identifies distinct outcomes in AML patients and is influenced by gemtuzumab ozogamicin. Oncotarget 2014;5(15):6280–8.

[20] Wadleigh M, Richardson PG, Zahrieh D, *et al.* Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. Blood 2003;102(5):1578–1582.

[21] Hütter-Krönke M-L, Benner A, Döhner K, *et al.* Salvage therapy with high-dose cytarabine and mitoxantrone in combination with all-trans retinoic acid and gemtuzumab ozogamicin in acute myeloid leukemia refractory to first induction therapy. Haematologica 2016;101(7):839–45.
[22] Magwood-Golston JS, Kessler S, Bennett CL. Evaluation of gemtuzumab ozogamycin associated sinusoidal obstructive syndrome: Findings from an academic pharmacovigilance program review and a pharmaceutical sponsored registry. Leuk. Res. 2016;4461–4.
[23] Amakye D, Jagani Z, Dorsch M. Unraveling the therapeutic potential of the Hedgehog pathway in cancer. Nat. Med. 2013;19(11):1410–22.
[24] Irvine DA, Copland M. Targeting hedgehog in hematologic malignancy. Blood 2012;119(10):2196–2204.
[25] Thomas BJ. Cell-cycle control during development: taking it up a notch. Dev. Cell 2005;8(4):451–2.
[26] Straface G, Aprahamian T, Flex A, *et al.* Sonic hedgehog regulates angiogenesis and myogenesis during post-natal skeletal muscle regeneration. J. Cell. Mol. Med. 2009;13(8B):2424–35.
[27] Ruiz i Altaba A. Therapeutic inhibition of Hedgehog-GLI signaling in cancer: epithelial, stromal, or stem cell targets? Cancer Cell 2008;14(4):281–3.
[28] Gao J, Graves S, Koch U, *et al.* Hedgehog signaling is dispensable for adult hematopoietic stem cell function. Cell Stem Cell 2009;4(6):548–58.
[29] Kobune M, Iyama S, Kikuchi S, *et al.* Stromal cells expressing hedgehog-interacting protein regulate the proliferation of myeloid neoplasms. Blood Cancer J. 2012;2(9):e87.
[30] Fukushima N, Minami Y, Kakiuchi S, *et al.* Small-molecule Hedgehog inhibitor attenuates the leukemia-initiation potential of acute myeloid leukemia cells. Cancer Sci. 2016;107(10):1422–1429.
[31] Sadarangani A, Pineda G, Lennon KM, *et al.* GLI2 inhibition abrogates human leukemia stem cell dormancy. J. Transl. Med. 2015;13(1):98.
[32] Tauchi T, Okabe S, Katagiri S, *et al.* Targeting the Hedgehog Signaling Pathway By PF-04449913 Limits the Self-Renewal of MDS-Derived Induced Potent Stem Cells (iPSC): Molecular Mechanisms. Blood 2015;126(23):.
[33] Martinelli G, Oehler VG, Papayannidis C, *et al.* Treatment with PF-04449913, an oral smoothened antagonist, in patients with myeloid malignancies: a phase 1 safety and pharmacokinetics study. Lancet Haematol. 2015;2(8):e339–e346.
[34] Cortes JE, Heidel FH, Heuser M, *et al.* A Phase 2 Randomized Study of Low Dose Ara-C with or without Glasdegib (PF-04449913) in Untreated Patients with Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome. Blood 2016;128(22).
[35] Stone RM, Berg DT, George SL, *et al.* Postremission therapy in older patients with de novo acute myeloid leukemia: a randomized trial comparing mitoxantrone and intermediate-dose cytarabine with standard-dose cytarabine. Blood 2001;98(3):548–53.
[36] Röllig C, Bornhäuser M, Thiede C, *et al.* Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system. J. Clin. Oncol. 2011;29(20):2758–65.
[37] Wattad M, Weber D, Döhner K, *et al.* Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. Leukemia 2017;31(6):1306–1313.
[38] Schlenk RFF, Frech P, Weber D, *et al.* Impact of pretreatment characteristics and salvage strategy on outcome in patients with relapsed acute myeloid leukemia. Leukemia 2017;31(5):1217–1220.
[39] FDA. FDA Approves Gemtuzumab Ozogamicin for CD33-positive AML, 2017. [Online]. Available: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm574518.htm. [Accessed: 18-Jan-2017].
[40] EMA. International Council for Harmonization E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials Step 5, Date for coming into effect 30July 2020.

[41] Giesinger JM, Kieffer JM, Fayers PM, *et al.* Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J. Clin. Epidemiol. 2016;6979–88.
[42] Fayers P, Aaronson NK, Bjordal K, *et al. EORTC QLQ-C30 Scoring Manual*. European Organisation for Research and Treatment of Cancer, 2001.
[43] Buysse DJ, Reynolds CF, Monk TH, *et al.* Pittsburgh Sleep Quality Index., in *APA task force. Handbook of psychiatric measures*, Rush A. J. et al., Ed. Washington DC: APA, 2000, 678–680.
[44] Patient Health Questionnaire (PHQ) Screeners. INSTRUCTION MANUAL Instructions for Patient Health Questionnaire (PHQ) and GAD-7 Measures.
[45] Ware J, Snoww KK, Kosinski MA, Gandek BG (1993). SF36 Health Survey: Manual and Interpretation Guide. Lincoln, RI: Quality Metric, Inc. 1993. 30.
[46] Holm S. A Simple Sequentially Rejective Multiple Test Procedure. Scand. J. Stat. 1979;665–70.
[47] Schoenfeld D. The Asymptotic Properties of Nonparametric Tests for Comparing Survival Distributions. Biometrika 1981;68(1):316–319.
[48] Gupta S. Intention-to-treat concept: A review. Perspect. Clin. Res. 2011;2(3):109.
[49] Kahan BC, Harhay MO. Many multicenter trials had few events per center, requiring analysis via random-effects models or GEEs. J. Clin. Epidemiol. 2015;68(12):1504–1511.
[50] van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat. Methods Med. Res. 2007;16(3):219–242.
[51] Gray R. Flexible Method for Analyzing Survival Data Using Splines, with Applications to Breast Cancer Prognosis. J. Am. Stat. Assoc. 1992;87(420):942–951.
[52] Messerer D, Engel J, Hasford J, *et al.* Impact of different post-remission strategies on quality of life in patients with acute myeloid leukemia. Haematologica 2008;93(6):826–833.
[53] Brazier J, Roberts J, Deverill M (2002). The estimation of a preference-based measure of health from the SF-36. Journal of Health Economics. 21(2). 271–292.
[54] Warren E. Strengthening Research through Data Sharing. N. Engl. J. Med. 2016;375(5):401–403.
[55] Heuser, M, Ofran Y, Boissel N *et al.* Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol . 2020 Jun;31(6):697-712.
[56] Zeidan A, Schuster MW, Krauter J *et al.* pubmed Clinical Benefit of Glasdegib in Combination with Azacitidine or Low-Dose Cytarabine in Patients with Acute Myeloid Leukemia. Blood (2019) 134 (Supplement_1): 3916. DOI:10.1182/blood-2019-124034
[57] Kapp-Schwoerer S, Weber D, Corbacioglu A *et al.* Impact of gemtuzumab ozogamicin on MRD and relapse risk in patients with NPM1-mutated AML: results from the AMLSG 09-09 trial. Blood. 2020 Dec 24;136(26):3041-3050.

This protocol has been written using information from the following study protocols:

1. An open label phase 1b study of PF-04449913 (glasdegib) in combination with azacitidine in patients with previously untreated higher-risk myelodysplastic syndrome, acute myeloid leukemia or chronic myelomonocytic leukemia (EudraCT: 2014-001345-24)
2. A randomized (1:1), double-blind, multi-center, placebo controlled study evaluating intensive chemotherapy with or without glasdegib or azacitidine with or without glasdegib in patients with previously untreated acute myeloid leukemia (EudraCT: 2017-002822-19)

19 Appendixes

19.1 *ECOG*

ECOG	
Score	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

19.2 Response Criteria for Acute Myeloid Leukaemia

Category	Definition	Comment
Response		
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L (1000/μL); platelet count ≥100 × 10^9/L (100 000/μL)	MRD^{-} or unknown
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/μL]) or thrombocytopenia (<100 × 10^9/L [100 000/μL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment failure		
Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine (see Table 8) are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 d of death, without evidence of persistent leukemia	
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 d following its completion; or deaths occurring ≥7 d following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 mo
Progressive disease (PD)*,†	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 mo; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/μL], and/or platelet count to >50 × 10^9/L [50 000/μL] nontransfused); or • >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (>25 000/μL) (in the absence of differentiation syndrome)†; or • New extramedullary disease	Category mainly applies for older patient given low-intensity or single-agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC, absolute neutrophil count; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; WBC, white blood cell.

*The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

†Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

Source: Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424–447. [4]

19.3 WHO Myeloid Neoplasm and Acute Leukemia Classification

WHO myeloid neoplasm and acute leukemia classification [9]

Myeloproliferative neoplasms (MPN)
- Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
  - PMF, prefibrotic/early stage
  - PMF, overt fibrotic stage
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable

Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1,* or with *PCM1-JAK2*
- Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
- *Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2*

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^{-}$
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)
- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
  - MDS-RS and single lineage dysplasia
  - MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable
- *Provisional entity: Refractory cytopenia of childhood*

Myeloid neoplasms with germ line predisposition

Acute myeloid leukemia (AML) and related neoplasms
- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
  - AML with t(6;9)(p23;q34.1);*DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*

WHO myeloid neoplasm and acute leukemia classification [9]

Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Acute leukemias of ambiguous lineage

Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS

B-lymphoblastic leukemia/lymphoma

B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21

T-lymphoblastic leukemia/lymphoma

Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

19.4 Detailed Description of Study Visits (Day by Day)

		Induction therapy[1] (IT), one induction cycle											
PHASE	**Baseline**	**IT therapy**							**IT recovery, duration of 3-5 weeks**				**End of cycle**
DAY of Cycle [optional]	-14-0	1	2	3	4	5	6	7	15*	22*	[29*]	[36*]	EOC[2]
Clinical assessments													
Signs/symptoms	X												X
Vital signs	X^{Height}	X			X			X	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
Physical examination	X	X^{O}			X			X	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
ECG	X	X^{O}											
Extramedullary involvement	X												X
ECOG PS	X	X^{O}			X			X	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
Laboratory assessments													
Hematology	X	X^{SL}			X^{SL}			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Basic blood chemistry	X	X^{SL}			X^{SL}			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Extended blood chemistry & coagulation	X	X^{SL}			X^{SL}			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Local disease assessment	X												X
Central laboratory assessments													
Sample collection (BM, PB)	X								X^{optl}				X
MRD & Disease status	X												X
PROs and Health economics													
Patient Reported Outcomes & SF-36	X^{BI}												X
Resource utilization questionnaire													X
Treatment													
GO-147 (experimental arm)		X			X			X					
GO-1 (control arm)		X											
SOC: Cytarabine		X	X	X	X	X	X	X					
SOC: Daunorubicin		X	X	X									
Safety													
Concomitant medications & treatment	X	X	X	X	X	X	X	X	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
AE assessment		X	X	X	X	X	X	X	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
Pregnancy test (WOCBP only)	X	X^{O}											
Screening and Baseline													
Informed consent	X	**Footnotes:**											
Demographics	X	[1] conditional salvage therapy cycle (see next page) not considered											
Medical/oncologic history	X	[2] includes treatment-free recovery period of 3-5 weeks, may be omitted in case of ITSC.											
Genetic assessment (central lab)	X	* approximate number of day for assessments in weekly intervals (i.e. day given as calculated)											
Cytogenetics	X	BI=SF-36 plus background information											
ECHO	X	Height=at baseline incl. height in cm											
Abdominal ultrasound	X	optl=day 15 sample optional (may be taken instead at day 14/16/17/18, if necessary)											
Urinalysis	X	O=to be omitted if done within preceding 48h											
Virus diagnostics	X	SL=Safety lab, values not captured in eCRF											
Enrollment & Randomization	X	W=to be done in weekly intervals (preferably same day per week)											

		Induction therapy, one conditional[1] salvage therapy cycle (IT-SC) potentially added after the induction cycle												
PHASE	IT	**IT-SC therapy**							**IT-SC recovery**					**End of cycle**
DAY of Cycle [optional]	15/EOC	1	2	3	4	5	6	7	8	15*	22*	[29*]	[36*]	EOC[2]
Clinical assessments														
Signs/symptoms	X													X
Vital signs	X	X	X	X					X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
Physical examination	X	X^{O}							X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
ECG		X^{O}												
Extramedullary involvement	X													X
ECOG PS	X	X^{O}							X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
Laboratory assessments														
Hematology	X	X	X^{SL}	X^{SL}					$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Basic blood chemistry	X	X							$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Extended blood chemistry & coagulation	X								$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Local disease assessment	X							X						X
Central laboratory assessments														
Sample collection (BM, PB)	X													X
MRD & Disease status	X													X
PROs & Health economics														
Patient Reported Outcomes & SF-36	X													X
Resource utilization questionnaire	X													X
Treatment														
ST: High-dose Cytarabine		X	X	X										
ST: Mitoxantrone			X	X										
Safety														
Concomitant medications & treatment	X	X	X	X	X	X	X	X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
AE assessment	X	X	X	X	X	X	X	X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
Pregnancy test (WOCBP only)		X^{O}												

Footnotes:

[1] in case of IT day 15 bone marrow blast count >10% or no CR/CRi after the induction therapy cycle

[2] includes treatment-free recovery period

* approximate number of day for assessments in weekly intervals (i.e. day given as calculated)

O=to be omitted if done within preceding 48h

SL=Safety lab, values not captured in eCRF

W=to be done in weekly intervals (preferably same day per week)

		Consolidation Therapy (CT), two cycles																		
PHASE	**IT**	**CT cycle 1**							**CT recovery [optional]**		**End of cycle**	**CT cycle 2**							**CT recovery [optional]**		**End of cycle**
DAY of Cycle [optional]	EOC	1	2	3	4	8*	15*	22*	[29*]	[36*]	EOC[1]	1	2	3	4	8*	15*	22*	[29*]	[36*]	EOC[1]
Clinical assessments																					
Signs/symptoms	X										X										X
Vital signs	X	X^{O}			X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X	X^{O}			X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
Physical examination	X	X^{O}			X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X	X^{O}			X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
ECG		X^{O}									X	X^{O}									X
Extramedullary involvement	X										X										X
ECOG PS	X	X^{O}									X	X^{O}									X
Laboratory assessments																					
Hematology	X	$X^{O,SL}$			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X	$X^{O,SL}$			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Basic blood chemistry	X	$X^{O,SL}$			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X	$X^{O,SL}$			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Ext. blood chemistry & coagulation	X	$X^{O,SL}$			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X	$X^{O,SL}$			X^{SL}	$X^{SL,W}$	$X^{SL,W}$	$X^{SL,W}$	[$X^{SL,W}$]	[$X^{SL,W}$]	X
Local disease assessment																					X
Central laboratory assessments																					
Sample collection (BM, PB)	X										X										X
MRD & Disease status	X										X										X
PROS & Health economics																					
Patient Reported Outcomes & SF-36	X										X										X
Resource utilization questionnaire	X										X										X
Treatment																					
SOC: Cytarabine		X	X	X								X	X	X							
Glasdegib/Placebo		daily from cycle day 1 to 28										daily from cycle day 1 to 28									
Unblinding																					X
Drug Compliance											X										X
Safety																					
Concomitant medi-cations & treatment	X	X	X	X	X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X	X	X	X	X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
AE assessment	X	X	X	X	X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X	X	X	X	X	X^{W}	X^{W}	X^{W}	[X^{W}]	[X^{W}]	X
Pregnancy test (WOCBP only)		X										X									X

Footnotes:

[1] includes treatment-free recovery period of up to 2 weeks if needed

* approximate number of day for assessments in weekly intervals (i.e. day given as calculated)

O=to be omitted if done within preceding 48h

SL=Safety lab, values not captured in eCRF

W=to be done in weekly intervals (preferably same day per week)

		Maintenance Therapy (MT), six cycles												
PHASE	**CT**	**MT cycle 1**		**MT cycle 2**		**MT cycle 3**		**MT cycle 4**		**MT cycle 5**		**MT cycle 6**		**End of treat-ment**
DAY of Cycle	**EOC**	1-27	28/ EOC	1-27	28/ EOC	1-27	28/ EOC	1-27	28/ EOC	1-27	28/ EOC	1-27	28/ EOC	EOT
Clinical assessments														
Signs/symptoms	X						X						X	X^{O}
Vital signs	X		X		X		X		X		X		X	X^{O}
Physical examination	X		X		X		X		X		X		X	X^{O}
ECG	X		X		X		X		X		X		X	X^{O}
Extramedullary involvement	X						X						X	X^{O}
ECOG PS	X		X		X		X		X		X		X	X^{O}
Laboratory assessments														
Hematology	X		X		X		X		X		X		X	X^{O}
Basic blood chemistry	X		X		X		X		X		X		X	X^{O}
Ext. blood chemistry & coagulation	X		X		X		X		X		X		X	X^{O}
Local disease assessment							X						X	X^{O}
Central laboratory assessments														
Sample collection (BM, PB)	X						X						X	X^{O}
MRD & Disease status	X						X						X	X^{O}
PROs & Health economics														
Patient Reported Outcomes & SF-36	X						X						X	$X^{BI,O}$
Resource utilization questionnaire	X						X						X	X^{O}
Treatment														
Glasdegib / SOC^{PhC}	(X)	X^{D}	X	X^{D}	X	X^{D}	X	X^{D}	X	X^{D}	X	X^{D}	X	
Drug Compliance	X		X		X		X		X		X		X	X^{O}
Safety														
Concomitant medi-cations & treatment	X		X		X		X		X		X		X	X
AE assessment	X		X		X		X		X		X		X	X
Pregnancy test (WOCBP only)	X		X		X		X		X		X		X	X^{O}

Footnotes:

BI=SF-36 plus background information

D=daily

O=to be omitted if done within preceding 48h

SOC^{PhC} =Standard of Care according to Physician's Choice

		Safety follow-up (SA) and observational follow-up (FU)								
PHASE	**MT**	**Safety follow-up**		**Observational follow-up (FU)**						**End of study**
Weeks (W)/ Months (M) from EOT [optional]	EOT	W4	W8	M3	M6	M9	M12	M15	[3-month intervals starting with M18]	EOS
Clinical assessments										
Signs/symptoms	X[O]	X	X	X	X	X	X	X	X[Y]	X
Vital signs	X[O]	X	X	X	X	X	X	X	X[Y]	X
Physical examination	X[O]	X	X	X	X	X	X	X	X[Y]	X
ECG	X[O]									X
Extramedullary involvement	X[O]			X	X	X	X	X	X[Y]	X
Patient Reported Outcomes	X[O]			X	X	X	X	X	X[Y]	X
ECOG PS	X[O]	X	X	X	X	X	X	X	X[Y]	X
Laboratory assessments										
Hematology	X[O]	X	X	X	X	X	X	X	X[Y]	X
Basic blood chemistry	X[O]	X	X	X	X	X	X	X	X[Y]	X
Extended blood chemistry & coagulation	X[O]	X	X							
Local disease assessment				X	X	X	X	X	X[Y]	X
Central laboratory assessments										
Sample collection (BM, PB)	X[O]			X	X	X	X	X	X[Y]	X
MRD & Disease status	X[O]			X	X	X	X	X	X[Y]	X
Safety										
Concomitant medications & treatment	X									
AE assessment	X	X	X							
Pregnancy test (WOCBP only)	X[O]	X	X							

Footnotes:

O=to be omitted if done within preceding 48h

Y=after 2 years from study day 1, on- site visits are no longer mandatory and may be replaced by contacting the treating physician or mailing the questionnaire. In this case, no further samples are collected.