KURZPROTOKOLL
BRIGHT

Öffentlicher Titel	Phase I Studie zu Glasdegib bei unbehandelten hämatologischen Neoplasien
Wissenschaftl. Titel	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
Kurztitel	BRIGHT
Studienart	multizentrisch, prospektiv, Therapiestudie, offen/unverblindet, Pharma-Studie, zweiarmig
Studienphase	Phase I
Erkrankung	Blut: Myeloische Neoplasien/Dysplasien: Chronische myelomonozytäre Leukämie (CMML) Blut: Myeloische Neoplasien/Dysplasien: Myelodysplastische Syndrome (MDS) Blut: Akute myeloische Leukämie (AML): Neu diagnostiziert / de novo
Einschlusskriterien	- Patients must have previously untreated MDS or AML according to the WHO 2016 classification. (Appendix 17). - a) The following AML patients will be included: - -> AML arising from MDS or another antecedent hematologic disease (AHD); - -> AML after previous cytotoxic therapy or radiation (secondary AML). - b) MDS patients must have Intermediate (>3 to 4.5 points), High-Risk (>4.5 – 6) or Very High-Risk (>6 points) disease according to the Revised International Prognostic Scoring System 2012 (IPSS-R). (Appendix 10). - -> CMML patients according to the WHO 2016 classification (Appendix 17) are included in the MDS cohort; - -> MDS/MPN, unclassifiable patients according to the WHO 2016 classification (Appendix 17) are included in the MDS cohort - Clinical indication for treatment with azacitidine for MDS or AML - >=18 years of age - Adequate organ function as defined by the following: - -> Total serum bilirubin <=2 x ULN, unless the bilirubin is principally unconjugated and there is strong suspicion of sub-clinical hemolysis or the patient has documented Gilbert's disease (patients with a history of Gilbert's disease are eligible if the direct bilirubin level is not greater than 0.5 mg/dL) - -> Aspartate transaminase (AST) and Alanine transaminase (ALT) <=3 x ULN, excluding patients with liver function abnormalities due to underlying malignancy; - -> Estimated creatinine clearance 30 mL/min as calculated using the standard method for the institution - Serum or urine pregnancy test (for female patients of childbearing potential) with a minimum sensitivity of 25 IU/L or equivalent units of human chorionic gonadotropin (HCG) negative at screening. - Male and female patients of childbearing potential and at risk for pregnancy must agree to use at least (1) highly effective method(s) of contraception throughout the study and for 180 days after the last dose of azacitidine and the last dose of glasdegib, whichever occurs later. - Female patients who are not of childbearing potential must meet at least 1 of the following criteria: - a) Have undergone a documented hysterectomy and/or bilateral oophorectomy; - b) Have medically confirmed ovarian failure; or

- c) Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women. All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.
- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
- Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures (including BM assessments).

Ausschlusskriterien

- Acute Promyelocytic Leukemia (APL) patients (French-American-British [FAB] M3 classification) with t(15;17) or APL with promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) (WHO 2016 classification).
- Patients with a known t(9:22) cytogenetic translocation (AML with BCR-ABL1) as a sole abnormality.
- Patients with AML who are candidates for standard induction chemotherapy as first line treatment
- Patients with known active CNS leukemia
- Prior treatment with a smoothened inhibitor (SMOi) and/or hypomethylating agent
- Participation in a clinical study involving an investigational drug(s) (Phases 1-4) within 4 weeks prior to study entry
- Major surgery or radiation within 12 weeks prior to study entry for safety LIC, 4 weeks in the expansion component
- 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
- Current use or anticipated requirement for drugs that are known strong CYP3A4/5 inducers
- Diagnosis of any active malignancy on treatment with the exception of adequately treated: (i) in-situ carcinomas, (ii) basal or squamous cell carcinoma, or (iii) non-melanoma skin cancer. Other prior or concurrent malignancies will be considered on a case-by-case basis
- Known malabsorption syndrome or other condition that may impair the absorption of the study drug (eg, gastrectomy, lap band, Crohn's disease) and inability or unwillingness to swallow tablets or capsules.
- Patients with an active, life threatening or clinically significant uncontrolled systemic infection
- Current drug or alcohol abuse
- Any one of the following ongoing or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de pointes, symptomatic arrhythmias (including sustained ventricular tachyarrhythmia), left bundle branch block or bifascicular block, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association class III or 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)
- Pregnant or breastfeeding female patients

	- Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study - Documented or suspected hypersensitivity to azacitidine or mannitol - Other severe acute or chronic medical or psychiatric conditions, including recent (within the past year) or active/ongoing suicidal ideation or behavior, or laboratory abnormalities that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and that in the judgment of the investigator, would make the patient inappropriate for entry into the study
Alter	18 Jahre und älter
Sponsor	Pfizer
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT02367456 (primäres Register) EudraCT 2014-001345-24