Kompetenznetz "Akute und chronische Leukämien"

KURZPROTOKOLL

DECLINE

Öffentlicher Titel	Phase IIIb Studie zur Bestimmung der Konversionsrate von MMR zu MR >= 4 log bei CML
Wissenschaftl. Titel	Imatinib 400 mg Daily vs Nilotinib 300 mg Twice Daily in Patients With Chronic Myeloid Leukemia in 1st Chronic Phase and Confirmed Major Molecular (MMR) Response Receiving Imatinib at a Dose of 400 mg Daily.
Kurztitel	DECLINE
Studiennummer KN/ELN	LN_NN_2014_562
Studiengruppe	NN
Studienart	randomisiert, prospektiv, offen, zweiarmig
Studienphase	Phase III
Erkrankung	Chronische myeloische Leukämie (CML) - Chronische Phase
Leukämiestadium	Komplette molekulare Remission (MR4)
Molekularer Marker	BCR-ABL
Ziele	- Goal of the study is to investigate whether in patients with CML in chronic phase and confirmed MMR receiving Imatinib at 400 mg daily a switch to Nilotinib at 300 mg twice daily results in a higher proportion of patients with confirmed conversion from MMR to MR4 after two years of study treatment when compared with patients who continue receiving Imatinib (400 mg daily). - To determine the cumulative incidence of MR4 and MR4.5 after one and two years - To determine the proportion of patients with MR4 and MR4.5 lasting for at least one and two years - To determine the kinetics of BCR-ABL transcript levels over time - To determine the proportion of patients with confirmed conversion from MMR to MR4 two years after cross-over from Imatinib to Nilotinib in patients failing the primary endpoint in the Imatinib arm - To determine whether baseline clinical data are informative with respect to MMR to MR4 conversion - To investigate the predictive value of a previously developed mathematical model of CML treatment with respect to the patient-specific probability of reaching MR4 under continuous Imatinib - To collect data to establish a mathematical model regarding the prediction ac-curacy of the molecular relapse probability after treatment discontinuation - To determine changes in the health-related Quality of Life - Study drug compliance
Haupt- und Nebenzielkriterien	- name
Einschlusskriterien	- 1. Signed written informed consent - 2. Male or female patients aged >=18 years (without upper limit of age) - 3. ECOG performance status of 0 to 2 - 4. CML in 1st chronic phase, with chronic phase defined as blasts < 15% in blood and/or bone marrow and peripheral blood basophils < 20% and platelets 100 G/L - 5. Pretreatment with Imatinib with a treatment duration of at least 2 years - 6. Imatinib treatment with a a current dosage of 400 mg to 600 mg daily

- 7. Molecular inclusion criteria: a. Molecular response with BCR-ABL/control gene ratio > 0.005% and <= 0.2% receiving Imatinib at 400 mg daily at most recent assessment during 6 months before informed consent will qualify for screening b. Major molecular response (MMR) without molecular response >= 4 log (MR4), i.e. BCR-ABL/control gene > 0.01% and <= 0.1% IS con-firmed by central laboratory at screening will be required for randomisation
- 8. Patients must have a serum Creatinine of <= 1.5 x ULN, SGOT <= 1.5 x ULN, total bilirubin <= 1.5 x ULN (except known M. Gilbert), and Lipase <= 1.5 x ULN
- 9. Women of child-bearing potential defined as sexually mature women who have not undergone a hysterectomy or who have not been natural-ly postmenopausal for at least 12 consecutive months, must have a negative serum pregnancy test during screening period. Male and fe-male patients of reproductive potential must agree to employ highly ef-fective methods of birth control throughout the study and for up to 3 months following discontinuation of study drug. Appropriate methods are e.g. a highly effective method of first choice, i.e. a method with a low failure rate (less than 1% per year) like sexual abstinence, combined oral contraceptives, implants, injectable, some Intra Uterine De-vices (IUDs), vasectomized partner, in combination with a method of second choice like condom, diaphragm, or cup pessary with spermi-cidal foam/gel/film/cream/suppository.

Ausschlusskriterien

- 1. Any previous treatment for CML other than Hydroxyurea, Imatinib or Interferon alpha
- 2. Evidence of features of accelerated or blast phase at any time (for more details see chapter 5.2)
- 3. Previous loss of hematologic or cytogenetic response
- 4. Concomitant medications known to be strong inducers or inhibitors of P450 Isoenzyme CYP3A4 (see Cytochrome P450 Drug Interaction un-der www.drug-interaction.com)
- 5. Finding of a secondary BCR-ABL resistance mutation at any time
- 6. History of intolerance to Imatinib that required treatment interruption longer than 4 weeks (cumulative) or dose reductions to less than 400 mg daily for longer than 4 weeks (cumulative) during the last 12 months before informed consent
- 7. Patients who had prior allogeneic, syngeneic, or autologous bone mar-row transplant or stem cell transplant
- 8. Patients unwilling to or unable to comply with the planned therapeutic intervention or to comply with the study treatment visits including blood sample collection within the protocol
- 9. History of pancreatitis, chronic inflammatory diseases or autoimmune diseases
- 10. Patients who underwent solid organ transplantation
- 11. Impaired cardiac function, including any of the following: - History of or presence of complete left bundle branch block, right bundle branch block plus left anterior hemi block, bifascicular block in screening ECG - Use of a cardiac pacemaker - ST depression of > 1mm in 2 or more leads and/or T wave inver-sions in 2 or more contiguous leads in screening ECG - Congenital Long QT Syndrome - QTc > 450 msec in the screening ECG - QT prolonging concomitant medication - History of or presence of significant ventricular or atrial tachy-arrhythmia in screening ECG - History of or presence of clinically significant resting bradycardia (< 50 beats per minute) - Myocardial infarction within 12 months prior to informed consent - Unstable angina diagnosed or treated during the past 12 months before informed consent - Other clinically significant heart disease (e.g., congestive heart fail-ure, uncontrolled hypertension, history of labile hypertension)
- 12. Known HIV and/or hepatitis B or C infection (testing is not mandatory)

- 13. Other malignancies within the past 3 years before informed consent except for adequately treated carcinoma of the cervix and basal or squamous cell carcinoma of the skin
- 14. Women who are pregnant or breast feeding
- 15. Male/female patients of reproductive potential unwilling to practice a highly effective method of birth control

Alter	>= 18 Jahre
Status	Aktiv
Beginn der Rekrutierung	01.09.2014
Rekrutierende Länder	Deutschland
Fallzahl	132
Studienleiter/in	von Bubnoff, Prof.Dr., Nikolas University Medical Center E-Mail: nikolas.bubnoff@uniklinik-freiburg.de
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Registrierung in anderen Studienregistern	ClinicalTrials.gov02174445 European Clinical Trials Database - EUDRACT2013-000077-68
Anmerkung	Primary end point: Proportion of patients with confirmed conversion from MMR to MR4 after two years of study treatment. Confirmed conversion from MMR to MR4 is defined as either BCR-ABL/ABL 0.01% IS at 21 and 24 months or BCR-ABL/ABL 0.01% IS at 24 months and confirmation within six weeks. (Month 21 and 24) Secondary end points: • Cumulative incidence of MR4 and MR4.5 after one and two years of study treatment • Proportion of patients with MR4 lasting for at least one year, defined as BCR-ABL/ABL <= 0.01% IS in at least three out of four consecutive 3-monthly meas-urements with first and last measurement showing MR4 • Proportion of patients with MR4 lasting for at least two years, defined as BCR-ABL/ABL <= 0.01% IS in at least six out of eight consecutive 3-monthly meas-urements with first and last measurement showing MR4 • Proportion of patients with MR4.5 lasting for at least one year, defined as BCR-ABL/ABL <= 0.0032% IS in at least three out of four consecutive 3-monthly measurements with first and last measurement showing MR4,5 • Proportion of patients with MR4.5 lasting for at least two years, defined as BCR-ABL/ABL <= 0.0032% IS in at least six out of eight consecutive 3-monthly measurements with first and last measurement showing MR4,5 • Kinetics of BCR-ABL transcript levels over time • Proportion of patients with confirmed conversion from MMR to MR4 two years after cross-over from Imatinib to Nilotinib in patients failing the primary end-point in the Imatinib arm (patients failing to achieve confirmed MMR to MR4 conversion two years after randomization and continued treatment with Imatinib) • Analysis of baseline clinical data which are informative with respect to MMR to MR4 conversion • Application of a previously developed mathematical model to predict the pa-tient-specific probability of reaching MR4 under continuous Imatinib • To establish a mathematical model to predict molecular relapse probability af-ter treatment discontinuation (to be validated in DECLINEplus) • Analysis of changes in the health-related Quality of Life (EORTC-QLQ-C30, EORTC-QLQ-CML24) • Study drug compliance (patient diary)