|  |  |
| --- | --- |
| TRIAL TITLE | Persistence of major molecular remission (MR3) in chronic myeloid leukemia after a second stop of TKI treatment in patients who failed an initial stop attempt. |
| SPONSOR | Uppsala University Hospital, Uppsala, Sweden |
| INVESTIGATORS | **Main investigators and members of study steering committee:**  **Ulla Olsson-Strömberg**, Department of Hematology, Uppsala University Hospital, Uppsala, Sweden  **Jeroen Janssen,** Dept. of Hematology, VU University Medical Center, Amsterdam, The Netherlands  **Lydia Roy**, Service d’Hématologie Clinique, Centre Hospitalo-Universitaire Henri Mondor Créteil, France  **Dominik Wolf**, Universitätsklinikum Bonn Medizinische Klinik 3Onkologie, Hämatologie und Rheumatologie, Bonn, Germany  **Henrik Hjorth-Hansen,** Department of Hematology, St Olavs Hospital Trondheim, Norway  **Waleed Majeed Mohammed**, Department of Blood and Cancer diseases  Stavanger University Hospital, Stavanger, Norway  **Johan Richter,** Dept. of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden  **Satu Mustjoki** Hematology Research Unit Helsinki, Department of Hematology, University of Helsinki and Helsinki University Central Hospital Comprehensive Cancer Center, Helsinki, Finland  **Perttu Koskenvesa** Hematology Research Unit Helsinki, Department of Hematology, University of Helsinki and Helsinki University Central Hospital Comprehensive Cancer Center, Helsinki, Finland  **Andreja Dimitrijevic**, Department of Hematology, Odense University Hospital, Odense, Denmark  **Jesper Stentoft**, Department of Hematology, Aarhus University Hospital, Aarhus, Denmark  **Co-Investigators:** See appendix. |
| BIOSTATISTICIANS | Inger Persson, Uppsala, Sweden |
| MOLECULAR MONITORING | Hans Ehrencrona, Lund, Sweden |
| TRIAL DESIGN | Multicenter study, prospective, open label, uncontrolled. |
| OBJECTIVE | **Main objective:**  Assessment of treatment-free remission (persistence of MMR) after second attempt of TKI discontinuation in patients who failed a relapsed in the EURO-SKI study or under EURO-SKI like conditions. Patients must have received at least three years of further TKI treatment of which the two last years should be dasatinib. The patients must have been in MR4 for at least one year.  **Secondary objectives:**   1. Identification of clinical and biological factors correlating with the persistence of MMR or better after stopping TKI a second time. 2. Estimation of overall and progression free survival 3. Time to re-achievement of MR4 after restart of therapy following a second molecular relapse 4. Assessment of incidence of any AEs (e.g. from treatment related musculoskeletal AE ) that arise after stopping TKI treatment a second time**.** |
| PRIMARY END POINT | The proportion of patients maintaining MMR at 6 and 12 months after discontinuing TKI a second time (survival without loss of major molecular response, MMR, defined as BCR-ABL1 > 0.1% on IS at one time point). |
| SECONDARY  END POINTS | Assessment of:   1. Clinical and biological factors correlating with persistence of MMR or better after second TKI stop (BCR-ABL level before 2nd stop, Sokal score, gender, duration and type of TKI-treatment, duration of first TKI-stop, immunological biomarkers) 2. Number of patients who re-achieved stable MR4, and were offered study participation;.and Overall and progression-free survival and the occurrence of a restart of TKI without prior molecular relapse . 3. Time to reachievement of MR4 after second loss of MMR. 4. Adverse events related to second TKI stop, clinical and biological factors correlated to development of these AEs. |
| INCLUSION CRITERIA-  SHORT | 1. CML in CP under TKI treatment after failing a prior attempt to stop treatment within EURO-SKI or outside the study but according to EURO-SKI trial procedures. For the latter group this requires at least 3 years of TKI treatment (first line or second line due to intolerance to first line) before first stop, and MR4 for at least one year before stopping. 2. Treated with TKI for at least one year after having failed a prior attempt to stop TKI. Previous TKI can be any. 3. Typical BCR/ABL1 transcript (b3a2 and/or b2a2) must have been confirmed at diagnosis or later during the disease course.   4. 18 years or older. |
| EXCLUSION CRITERIA | 1. Previous hematological relapse after first stop of TKI. 2. Previous AP/BC at any time in the history of the disease. 3. Restart of TKI without loss of MMR after first stop 4. Current participation in another clinical study. 5. Previous or planned allogeneic stem cell transplantation. 6. Patients with contra-indications to dasatinib therapy due to comorbidities. 7. Subjects with acute hepatitis B virus (HBV) infections. 8. Uncontrolled or significant cardiovascular disease. 9. Pulmonary arterial hypertension. 10. Pleural or pericardial effusions of any grade at study entry are excluded 11. History of significant bleeding disorder unrelated to CML 12. Hypersensitivity to dasatinib and excipients of dasatinib tablets. |
| TRIAL PROCEDURES AND MONITORING OF PATIENTS | **Trial procedures:**   1. After inclusion in 2nd Stop, patients will be treated with dasatinib at a starting dose of 70-100 mg/day at the discretion of the investigator or 100 mg/day 5 days/week with dose reduction to 50 mg/day if side effects occur.If the patient have been treated with 50 mg once daily before entering the study ,it is possible for the patient to enter the study at this dose, if the patient is in deep molecular response (MR4). 2. After a total of 3 years of post-relapse of TKI treatment of which the last 2 years should be with dasatinib, patients are eligible for a second stop attempt if they also have re-achieved and maintained stable MR4 during the last 12 months before 2nd discontinuation attempt. 3. Before dasatinib is stopped, MR4 should be confirmed and TKI therapy should be stopped within 6 weeks of this MR4 confrimation. 4. After 2nd TKI discontinuation, patients are monitored as follows: Hematological monitoring and q-RT-PCR of BCR/ABL1: Month 1-6 monthly, month 7-12 every 1.5 months, and thereafter once every three months. Clinical monitoring every 3 months during 3 years. 5. Relapse is defined as BCR-ABL1 >0.1% on I.S. at a single time point (loss of MMR/MR3) and should lead to immediate restart of TKI, type and dose at the discretion of the treating physician. 6. If relapse occurs, the patient could countinue with dasatinib during one year on study (study drug). |
| TRIAL DURATION | 2 years for inclusion of patients, 2 years with dasatinib treatment and 3 years of follow-up. |
| NUMBER OF PATIENTS | 111 patients needed for substudies in total for core and substudies.  Compensation for drop outs: 23 additional patients to be included in clinical core study. This is based on the percentage of patients stopping treatment in the Dasision study for factors due to intolerance, treatment failure and “other reasons” (Jabbour 2014) |
| PROPOSED SUB-STUDIES | 1. Immunophenotyping of lymphocyte subsets. 2. Assessment of antileukemic cytotoxic T-cell responses. 3. Plasma cytokine profiling. 4. Functional assessments of NK and T cells. 5. Immunological monitoring-plasmacytoid DCs. 6. Evaluation of soluble CD62L levels and TACE. activity as relapse risk sensing tools. 7. TCR repertoire analysis by deep sequencing. 8. Kir genotyping. 9. Cytof-based Immune-phospho-flow cytometry |
| STUDY MILESTONE DATES | Study start: MARCH 2017.  Recruitment end: Q4 2018.  Study end: Q4 2020. |