The Ruxo-BEAT Trial in Patients With High-risk Polycythemia Vera or High-risk Essential Thrombocythemia (Ruxo-BEAT)

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2015 by RWTH Aachen University

Sponsor:
RWTH Aachen University

Collaborator:
Novartis

Information provided by (Responsible Party):
RWTH Aachen University

ClinicalTrials.gov Identifier:
NCT02577926

First received: October 1, 2015
Last updated: November 5, 2015
Last verified: October 2015
History of Changes

Purpose

The Philadelphia chromosome negative myeloproliferative neoplasms (MPN) comprise a group of clonal hematological malignancies that are characterized by chronic myeloproliferation, splenomegaly, different degrees of bone marrow fibrosis, and disease-related symptoms including pruritus, night sweats, fever, weight loss, cachexia, and diarrhea. In addition, due to elevated numbers of leucocytes, erythrocytes and/or platelets, the disease course can be complicated by thromboembolic disease, hemorrhage, and leukemic transformation as well as myelofibrosis.

Patients with polycythemia vera (PV) typically harbor an increased number of blood cells from all three hematopoietic cell lineages due to clonal amplification of hematopoetic stem cells, while patients with essential thrombocythemia (ET) typically show a predominant expansion of the megakaryocytic lineage. Most patients with PV below the age of 60 years are currently being treated with acetylsalicylic acid +/- phlebotomy only, and patients with low-risk ET have an almost normal life expectancy and often do not require specific **treatment**. However, PV- as well as ET-patients with a higher risk for complications require cytoreductive **treatment**. In addition, constitutional symptoms can be unbearable to patients even in the absence of bona fide high risk factors, and these patients may similarly benefit from antineoplastic **therapy**.

Condition	Intervention	Phase
Polycythemia Vera (PV) Essential Thrombocythemia (ET)	Drug: **Ruxolitinib** Drug: BAT	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: **Ruxolitinib Versus Best Available Therapy** in Patients With High-risk Polycythemia Vera or High-risk Essential Thrombocythemia - The Ruxo-BEAT Trial

Resource links provided by NLM:

Genetics Home Reference related topics: essential thrombocythemia polycythemia vera

Drug Information available for: Ruxolitinib Ruxolitinib phosphate

Genetic and Rare Diseases Information Center resources: Chronic Myeloproliferative Disorders Essential Thrombocythemia Polycythemia Vera

U.S. FDA Resources

Further study details as provided by RWTH Aachen University:

Primary Outcome Measures:

- The rate of complete clinicohematologic response rate (CHR) as defined by Barosi et al Blood 2009 [Time Frame: at month 6] [Designated as safety issue: No]

  The rate of complete clinicohematologic response rate (CHR) as defined by Barosi et al Blood 2009

Secondary Outcome Measures:

- Number of participants with **treatment**-related adverse events as assessed by CTCAE v4.0 [Time Frame: at month 6 and 12] [Designated as safety issue: Yes]
- The complete response rate (CR) at month 6 as defined by Barosi et al Blood 2013 (revised ELN response criteria) [Time Frame: month 6] [Designated as safety issue: No]
- The rate of complete responses (CHR) at month 12 as defined by Barosi et al Blood 2009 [Time Frame: month 12] [Designated as safety issue: No]
- The efficacy as assessed by the absence of phlebotomy (Hct <45%) [Time Frame: through study completion, an average of 2 years] [Designated as safety issue: No]
- The efficacy as assessed by the reduction in spleen size (palpable spleen that is reduced by > 50% from baseline measured by palpation and ultrasound) OR platelet count < 600 x 10^9/l (ET) [Time Frame: through study completion, an average of 2 years] [Designated as safety issue: No]
- Proportion of subjects achieving both durable absence of phlebotomy eligibility AND durable spleen volume reduction measured by palpation and ultrasound (PV) OR durable platelet count <600 x 10^9/l (ET) (durable defined as >3 months) {Barosi et al 2013) [Time Frame: through study completion, an average of 2 years] [Designated as safety issue: No]
- The rate of overall clinicohematologic remissions (CR + PR) according to both guidelines (Barosi et al 2009 and 2013) [Time Frame: through study completion, an average of 2 years] [Designated as safety issue: No]

Estimated Enrollment:	380
Study Start Date:	October 2015
Estimated Study Completion Date:	December 2020
Estimated Primary Completion Date:	December 2020 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: **Ruxolitinib** **Ruxolitinib** will be administered orally at a dose of 10 mg twice daily (both PV and ET) for two consecutive years.	Drug: **Ruxolitinib** **Ruxolitinib** is a JAK1/2-specific tyrosine kinase inhibitor (TKI) which has been approved for the **treatment** of symptomatic myelofibrosis. The compound was shown to be superior to hydroxyurea in reducing splenomegaly and constitutional symptoms. Other Names: • Study drug • Jakavi
Active Comparator: **Best available therapy** (BAT) BAT may include all currently used **treatment** options. BAT is at the choice of the investigator (monotherapy with i.e. hydroxyurea, anagrelide, interferon, busulfan, immunomodulators etc). BAT will be administrated for two consecutive years.	Drug: BAT BAT is at the choice of the investigator (monotherapy with i.e. hydroxyurea, anagrelide, interferon, busulfan, immunomodulators etc). Other Name: Controll **Treatment**

Detailed Description:

Polycythemia vera (PV) and essential thrombocythemia (ET) are classical Philadelphia-negative myeloproliferative neoplasms (MPN) that are characterized by an excess of cells in the peripheral blood, clonal bone marrow hyperplasia, and extramedullary hematopoiesis. The symptoms of these patients may range from asymptomatic disease to symptomatic disease that may significantly affect their activities of daily living, such as severe generalized pruritus, night sweats and fevers, erythromelalgia, bone and muscle pain, weight loss, and fatigue. Moreover, the patients may develop thromboembolic and hemorrhagic complications, transition to myelofibrosis (MF), and transformation to acute leukemia. In principle, the only potentially curative therapy for MPNs is allogenic stem cell transplantation (allo-SCT). However, due to

significant transplant-associated morbidity and mortality, this therapeutic option is only applied in exceptional cases of ET or PV. The majority of patients do not qualify for allo-SCT since the risks of this treatment clearly outw eigh the potential benefits. Moreover, even w ith a non-transplantation approach, patients w ith ET and PV have a life expectancy comparable to or close to healthy age-matched control persons. For patients w ith standard risk PV, phlebotomy and acetylsalicylic acid are standard of care (target hematocrit below 45 %), w hile patients w ith standard risk ET should receive either no specific treatment or acetylsalicylic acid (provided that no microvascular symptoms or secondary acquired von Willebrand syndrome are present).

How ever, in patients w ho are at high risk to develop thromboembolic or hemorrhagic complications (high-risk patients), cytoreductive treatment is generally indicated to prevent these potentially life-threatening complications. In PV and ET, high risk patients are characterized by advanced age (> 60 years) and / or a history of thromboembolic or hemorrhagic events {1,2,3}. In ET, a platelet count > 1500 x 109/l is associated w ith an increased risk of bleeding, and thus should result in a platelet low ering treatment {2}. In PV, in addition to the risk-score based therapy, cytoreduction is also required in patients w ith progressive or marked myeloproliferation (leukocytosis, thrombocytosis, symptomatic splenomegaly, increase of frequency of phlebotomy requirement), or devastating constitutional symptoms {1,2,4}. In Germany, best available therapy (BAT) includes approved drugs such as hydroxyurea (HU; approved for both PV and ET) and anagrelide (approved for second-line treatment of ET) and non-approved options such as alpha-interferon, pipobroman, busulfan (in elderly patients), and radioactive phosphorus (32P). In rare cases, patients may also benefit from splenic irradiation or splenectomy.

Ruxolitinib is a JAK1/2-specific tyrosine kinase inhibitor (TKI) w hich has been approved for the treatment of symptomatic myelofibrosis. The compound w as show n to be superior to hydroxyurea in reducing splenomegaly and constitutional symptoms. Ruxolitinib is currently studied in phase 2 and phase 3 clinical trials for HU-resistant or HU-intolerant PV and ET. The aim of the present study is to assess the feasibility, efficacy, and safety of ruxolitinib treatment vs. BAT in patients w ith high-risk PV or -ET.

Eligibility

Ages Eligible for Study:	18 Years and older
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. w ritten informed consent and w illing to comply w ith treatment and to follow up assessments and procedures
2. >18 years old
3. Patient´s ECOG performance status: 0-2
4. Patient must fulfill WHO 2008 diagnostic criteria for either PV or ET. PV- and ET-patients have to be classified as high risk according to defined criteria. For patients w ith high risk PV OR PV w ith indication for cytoreductive therapy due to progressive myeloproliferation, ANY ONE of the follow ing must be fulfilled:
   - Age >60 years
   - Previous documented thrombosis or thromboembolism
   - Platelet count > 1500 x 10^9/L
   - Poor tolerance of phlebotomy or frequent phlebotomy requirement
   - Symptomatic or progressive splenomegaly
   - Severe disease-related symptoms
   - Progressive leukocytosis w ith leukocyte count > 20 x 10^9/L

   For patients w ith high risk ET, ANY ONE of the follow ing must be fulfilled:
   - Age > 60 years
   - Platelet count> 1500 x 10^9/L
   - Previous thrombosis or thromboembolism
   - Previous severe hemorrhage related to ET.
5. Patients must fulfill the follow ing criteria regarding prior therapy:

PV patients: Never treated w ith cytoreductive drugs except hydroxyurea, anagrelide, or interferon for up to 6 w eeks maximum (phlebotomy and/or aspirin are allow ed) ET patients: Naïve and pretreated patients may be entered in this trial 7. adequate liver function, AST, and ALT ≤ 2 the institutional ULN value, unless directly attributable to the patient's MPN 8. creatinine clearance >40ml/min calculated according to the modified formula of Cockcroft and Gault, eGFR, or directly measured after 24h-urine collection 9. ability to sw allow and retain oral medication

Exclusion Criteria:

1. criteria for post PV-MF or post ET-MF are met
2. previous ruxolitinib treatment
3. history of anaphylaxis follow ing exposure to the BAT drug of choice
4. inadequate bone marrow reserve as demonstrated by ANC ≤ 1 x 10^9/l OR platelet count <50 x 10^9/l
5. know n hepatitis B or C or HIV infection

6. other severe, concurrent diseases, including tuberculosis, serious cardiac functional dysfunction (class III or IV), uncontrolled diabetes, uncontrolled hypertension, severe pulmonary disease, or major organ malfunction
7. history of active substance or alcohol abuse within the last year
8. Female patients who are pregnant or nursing
9. participation in another interventional trial and/or used investigational agents or concurrent anticancer treatment for concomitant disease within the last 4 weeks of registration
10. Any circumstances at the time the study entry that would preclude completion of the study or the required follow-up prohibits inclusion into this study
11. active malignancy during the previous 3 years except for treated cervical intraepithelial neoplasia, basal cell carcinoma of the skin, or squamous cell carcinoma of the skin, each with no evidence for recurrence in the past 3 years
12. active bacterial, viral, or fungal infection
13. medical condition requiring prolonged use of oral corticosteroids with a dose of more than 20 mg per day (> 1 month)
14. severe cerebral dysfunction and/or legal incapacity
15. history of active splanchnic vein thrombosis within the last 3 months (includes Budd-Chiari, portal vein, splenic and mesenteric thrombosis)
16. thyroid dysfunction which is not adequately controlled
17. Fertile men or women of childbearing potential cannot be included unless they are: surgically sterile or >2 years after the onset of menopause and/or willing to use a highly effective contraceptive method (Pearl Index <1)
18. patients who are taking any of the following prohibited medication: clarithromycin, telithromycin, troleandomycin, ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir -itraconazole, ketoconazole, voriconazole, fluconazole
19. Patients who suffer from galactose intolerance, lack of lactose or a glucose-galactose-malabsortion

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02577926

Contacts

Contact: Amrei Pelzer 00492418035768 apelzer@ukaachen.de

Contact: Verena Deserno +49241803380092 vdeserno@ukaachen.de

Locations

Germany

Uniklinik RWTH Aachen **Recruiting**
Aachen, NRW, Germany, 52074
Contact: Steffen Koschmieder, Univ.-Prof. Dr. med. 00492418036102 skoschmieder@ukaachen.de
Contact: Susanne Isfort, Dr-med. 00492418037411 sisfort@ukaachen.de

Universitätsklinikum Magdeburg **Recruiting**
Magdeburg, Sachesen-Anhalt, Germany, 39120
Contact: Florian Heidel, PD Dr. med. 0049 391 6713269 florian.heidel@med.ovgu.de

Sponsors and Collaborators

RWTH Aachen University

Novartis

Investigators

Principal Investigator: Steffen Koschmieder, Prof. Dr. RWTH University Hospital MK4

More Information

No publications provided

Responsible Party: RWTH Aachen University
ClinicalTrials.gov Identifier: NCT02577926 History of Changes

Other Study ID Numbers:	12-181
Study First Received:	October 1, 2015
Last Updated:	November 5, 2015
Health Authority:	Germany: Federal Institute for Drugs and Medical Devices

Additional relevant MeSH terms:

Polycythemia
Polycythemia Vera
Thrombocythemia, Essential
Thrombocytosis
Blood Coagulation Disorders
Blood Platelet Disorders
Bone Marrow Diseases
Hematologic Diseases
Hemorrhagic Disorders
Myeloproliferative Disorders

ClinicalTrials.gov processed this record on February 04, 2016