



MAJIC

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A RandoMised study of best Available therapy versus JAK Inhibition in patients with high risk Polycythaemia Vera or Essential Thrombocythaemia who are resistant or intolerant to HydroxyCarbamide

Trial Design

Phase II, randomised, open-label, two arm, multicentre clinical trial. The trial has two underlying hypotheses to investigate the activity of Ruxolitinib in two different patient populations. Randomisation will be stratified by each population and each hypothesis will be powered independently. Each research question will be analysed separately.

Objectives

To investigate and evaluate the activity and safety (in terms of complete haematological response within one year) of Ruxolitinib in the treatment of patients with Polycythaemia Vera (PV) or Essential Thrombocythaemia (ET) who have met criteria for resistance or intolerance of hydroxycarbamide (HC) therapy.

Sample Size

306 patients in total (190 with PV and 116 with ET) will be randomised.

Trial Duration

This trial opened in August 2012 and will recruit over 4 years. The primary endpoint will be assessed throughout year 1 and the time CR achieved will be recorded. Patients on the Ruxolitinib arm with complete or partial response at 1 year will continue therapy and be followed up for 5 years. Patients who do not achieve CR or PR with Ruxolitinib at 1 year and patients on the Best Available Therapy arm will also be followed up for 5 years.

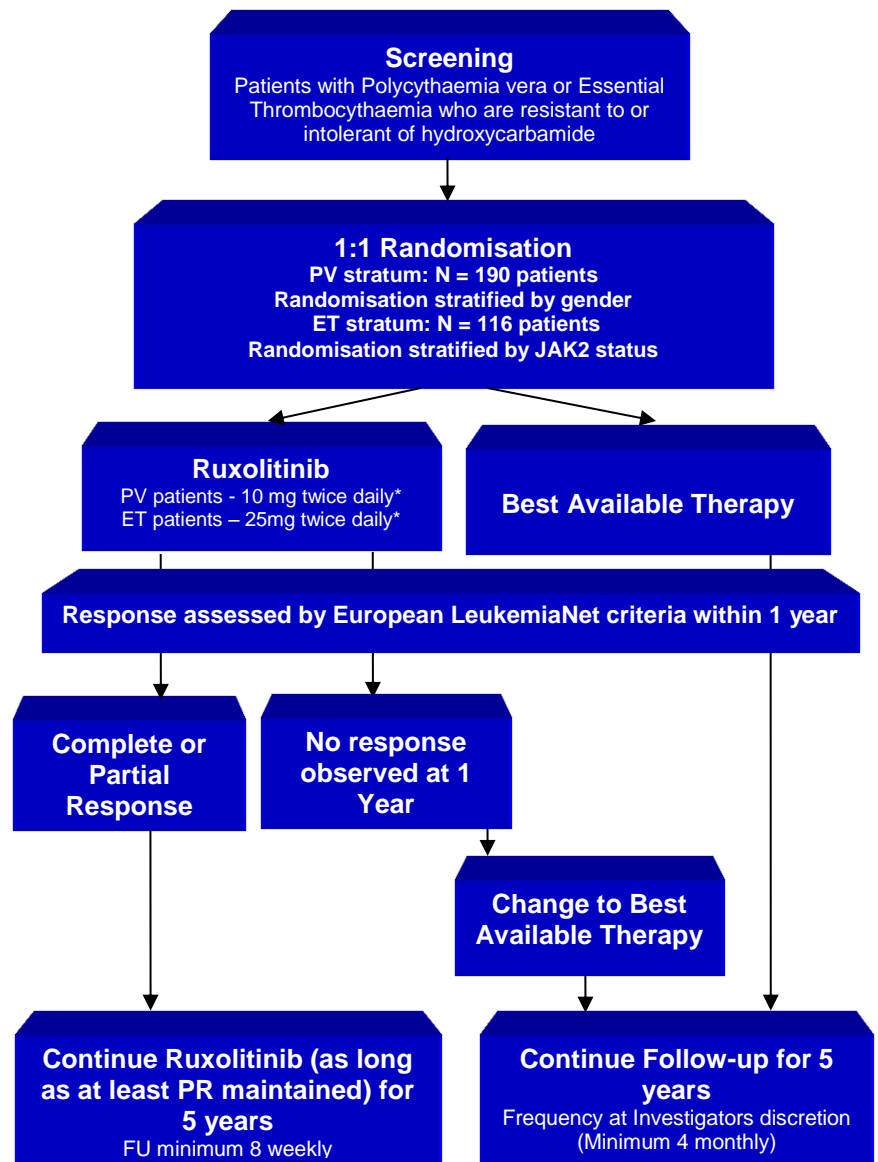
Outcome Measures

Primary Endpoints

Complete Response rates to Ruxolitinib as defined by European LeukemiaNet (ELN) criteria (within 1 year of treatment).

Secondary Endpoints

- Partial response rates as defined by ELN criteria within 1 year of treatment
- Duration of response
- Dose intensity
- Toxicity profile of Ruxolitinib based on CTC criteria
- Histological response: bone marrow biopsy analysis criteria as defined by ELN
- Molecular response: JAK2 V617F status quantitation; criteria defined by ELN
- Haemorrhagic and thromboembolic event rate
- Quality of life and disease symptom burden
- Overall survival
- Progression free survival



*Patients with platelet count between 100 and 200 x 10⁹/L will started on a reduced dose

Main Inclusion and Exclusion Criteria

Inclusion Criteria for PV

- Male or female patient ≥ 18 years of age
- A confirmed diagnosis of high risk* PV

*High Risk is defined as ANY ONE of the following:

- Age >60 years
- Previous documented thrombosis (including Transient Ischaemic Attack (TIA)), erythromelalgia or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered to be disease related
- Significant splenomegaly (i.e. $> 5\text{cm}$ below costal margin on palpation) or symptomatic (splenic infarcts or requiring analgesia)
- Platelets $> 1000 \times 10^9/\text{L}$
- Diabetes or hypertension requiring pharmacological therapy for > 6 months

Inclusion criteria for ET

- Male or female patient ≥ 18 years of age
- A confirmed diagnosis of high risk* ET

*High risk is defined as ANY ONE of the following:

- Age > 60 years
- Platelet count $> 1500 \times 10^9/\text{L}$
- Previous documented thrombosis (including Transient Ischaemic Attack (TIA)), erythromelalgia or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered to be disease related
- Previous haemorrhage related to ET
- Diabetes or hypertension requiring pharmacological therapy for > 6 months

ALL patients MUST ALSO be EITHER intolerant OR resistant to Hydroxycarbamide (HC) based on the following established criteria (Barosi, *et al.* 2007; Barosi,*et al.* 2010)

Any ONE of the following:

- Platelet count $>600 \times 10^9/\text{L}$ after 8 weeks of at least 2 g/day or MTD of HC (2.5 g/day in patients with a body weight >80 kg)
- Platelet count $>400 \times 10^9/\text{L}$ and WBC $< 2.5 \times 10^9/\text{L}$ at any dose of HC (for a period of at least 8 weeks)
- Platelet count $>400 \times 10^9/\text{L}$ and Hb < 110 g/L at any dose of HC (for a period of at least 8 weeks)
- Platelet count persistently $<100 \times 10^9/\text{L}$ at any dose of HC (for a period of at least 8 weeks)
- Progressive splenomegaly or hepatomegaly i.e. enlargement by more than 5cm or appearance of new splenomegaly or hepatomegaly on HC treatment
- Not achieving the desired reduction of haematocrit or packed cell volume with the addition of HC in patients who do not tolerate frequent venesections after 3 months of at least 2 g/day of HC (2.5 g/day in patients with a body weight >80 kg)
- Not achieving the desired stable reduction of WBC when leukocytes are a target of therapy after 8 weeks of at least 2 g/day or MTD of HC (2.5 g/day in patients with a body weight >80 kg)
- Thrombosis or haemorrhage (including Transient Ischaemic Attack (TIA)) while on therapy
- Presence of leg ulcers or other unacceptable HC-related non-haematological toxicities, such as unacceptable mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HC. OR Cycling platelet counts on therapy
- Disease related symptoms not controlled by hydroxycarbamide

The patient can have met any one of the above criteria AT ANY POINT in their disease whilst on Hydroxycarbamide.

ALL Patients Exclusion Criteria

- Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry)
- Patients and partners of childbearing potential not willing to use effective contraception
- ECOG Performance Status Score ≥ 3
- Uncontrolled rapid or paroxysmal atrial fibrillation, uncontrolled or unstable angina, recent (6 months) myocardial infarction or acute coronary syndrome or any clinically significant cardiac disease $> \text{NYHA Class II}$
- Patients who have transformed to myelofibrosis
- Previous treatment with Ruxolitinib
- Previous (within the last 12 months) or current platelet count $<100 \times 10^9/\text{L}$ or neutrophil count $< 1 \times 10^9/\text{L}$ not due to therapy.
- Inadequate liver function as defined by ALT/AST $>1.5 \times \text{ULN}$
- Inadequate renal function as defined by GFR < 30 mls/min
- Unable to give informed consent