TRIAL SYNOPSIS

A phase Ib study to assess the safety and tolerability of oral ruxolitinib in combination with 5-azacitidine in patients with advanced phase myeloproliferative neoplasms (MPN), including myelodysplastic syndromes (MDS) or acute myeloid leukaemia (AML) arising from MPNs.

Trial Design

A continual reassessment method (CRM) trial design to evaluate the Maximum Tolerated Dose (MTD) of ruxolitinib in combination with 5-azacitidine in patients with advanced phase MPN, including MDS or AML arising from MPNs. In addition, 30 patients that are unable or unwilling to enter the interventional component of the trial will be entered to a parallel observational component focussed on collecting information on patient demographics and outcomes.

Outcome Measures

Interventional Component

Primary

To determine the MTD of ruxolitinib in combination with 5-azacitidine in patients with advanced phase MPNs, including MDS or AML arising from MPNs using the CRM with a predefined target DLT probability of 25% within cycle 1 (days 1 - 28).

Main Secondary Outcomes

- Best response following 3 and 6 cycles of treatment.

Assessment will be made according to the following criteria:

  - "Proposed criteria for response assessment in patients treated in clinical trials for MPNs in blast phase (MPN-BP): Formal recommendations from the post-MPN acute myeloid leukaemia consortium" (for patients with ≥20% bone marrow blasts at baseline)[1]
  - International Working Group (IWG) response criteria in myelodysplasia (for patients with <20% bone marrow blasts at baseline)[2]

- Change in the proportion of patients who require transfusion of red cells or platelets after completion of cycles 3 and 6.
- Change in palpable splenomegaly or hepatomegaly
- Duration of Complete Response (CR) or Partial Response (PR)
- 12 months Overall survival (OS)

Observational Component

- To determine treatment and outcome of Accelerated Phase MPN (MPN-AP) and Blast Phase MPN (MPN-BP) patients
- Quality of life as measured by the MPN SAF; EQ-5D-5L and EORTC QLQ-C30 (at registration, 3 months and 6 months)

Exploratory (both components)

- Change in clonal marker (e.g. JAK2 or CALR allele burden) (to be centrally assessed)

Patient population and sample size

A maximum of 34 patients with advanced phase MPNs, including MDS or AML arising from MPN will be recruited to the interventional component over 36 months. Up to 30 patients will enter the observational component.

Main Inclusion and Exclusion Criteria

Inclusion Criteria:

Interventional Component

- Age ≥16 years old
- A prior diagnosis of Essential Thrombocythaemia (ET), Polycythaemia Vera (PV) or Myelofibrosis (MF) with one of the following:
  - 10-19% bone marrow blasts with or without dysplastic changes (MPN-AP) at baseline
  - ≥20% bone marrow Blasts (MPN-BP) at baseline
- In need of treatment in the opinion of the investigator
- Eastern Cooperative Oncology Group (ECOG) performance status 0-3
- Adequate liver and renal function, defined as:
  - Liver transaminases ≤3 × ULN (AST/SGOT or ALT/SGPT)

  - Bilirubin <4 x ULN (Patients with elevated bilirubin due to Gilbert's syndrome are eligible)
  - GFR ≥40 ml/min
- Willingness to undergo and ability to tolerate assessments during the study including bone marrow assessments and symptom assessments using patient reported outcome instruments
- Able to give valid informed consent

Observational Component

- Age ≥16 years old
- A prior diagnosis of ET, PV or MF with one of the following:
  - ≥10-19% blasts in blood or bone marrow with or without dysplastic changes (MPN-AP) at baseline
  - ≥20% blasts in blood or bone marrow (MPN-BP) at baseline
- Patients who are unwilling/unable to enter the interventional component and/or fail the interventional component entry criteria. This can include patients previously treated post transformation into MPN-AP/MPN-BP, or entered into studies with more aggressive therapy such as AML 17/19 as well as those receiving palliation only.
- Able to give valid informed consent

Exclusion Criteria:

Interventional Component:

- Any co-morbidity that could limit compliance with the trial or any other condition (including laboratory abnormalities) that in the Investigators opinion will affect the patient's participation in this trial
- New York Heart Association Class II, III, or IV congestive heart failure
- On-going cardiac dysrhythmias of grade 3, QTc prolongation >480 ms, or other factors that increase the risk of QT interval prolongation (e.g. heart failure, hypokalemia defined as serum potassium <3.0 mEq/L, family history of long QT interval syndrome)
- Erythropoietic agent within 28 days prior to registration
- Thrombopoietic agent within 14 days prior to registration
- Potent CYP3A4 inhibitor within 7 days prior to registration
- Experimental treatment within 14 days prior to registration.
- Previous treatment for MPN-AP or MPN-BP, including stem cell transplant and low intensity AML chemotherapy
- Previously received 5-azacitidine. Ruxolitinib can be taken up until study entry at the pre-study dose. Hydroxycarbamide prescribed prior to study entry must be stopped before the first scheduled day of trial treatment
- Known contraindications to receiving 5-azacitidine or ruxolitinib
- Active infection ≥ grade 3 (CTCAE criteria) at trial entry
- Known HIV seropositivity
- Known to have active hepatitis A, B, or C
- Women who are pregnant or lactating. 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 for the duration of the study treatment and for three months after the last dose

Observational Component

- No Exclusions.

Trial Duration

All patients on the interventional component will receive a minimum of 6 cycles of treatment and will be followed up for a further 6 months (total of 12 months from registration). Patients will continue therapy if they receive a clinical benefit at the discretion of the CI. Patients on the observational component will be assessed over a 6 month period and will be followed up for survival data for a minimum of 1 year from the date of registration. Recruitment will be over 36 months. Therefore the total trial duration will be 48 months.

Trials Office Contact Details

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