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# Assessing 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 MPN.

**Submission date**
18/03/2015

**Recruitment status**
No longer recruiting

**Registration date**
19/03/2015

**Overall study status**
Completed

**Last Edited**
17/08/2023

**Condition category**
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

**Plain English summary of protocol**
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-azacitidine-and-ruxolitinib-for-blood-disorders-called-myeloproliferative-neoplasms

## Contact information

**Type(s)**
Scientific

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## Additional identifiers

**Clinical Trials Information System (CTIS)**
2014-002563-16

**Protocol serial number**
18136

# Study information

**Scientific Title**
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 MPN

**Acronym**
PHAZAR

**Study objectives**
To establish the maximum tolerated dose (MTD) and safety of ruxolitinib in combination with 5-azacitidine

**Ethics approval required**
Old ethics approval format

**Ethics approval(s)**
NRES Committee West Midlands - Edgbaston,19/01/2015, ref: 14/WM/1260

**Study design**
Non-randomised; Interventional; Design type: Treatment

**Primary study design**
Interventional

**Study type(s)**
Treatment

**Health condition(s) or problem(s) studied**
Myeloproliferative neoplasms (MPN), including myelodysplastic syndromes (MDS) or acute myeloid leukaemia (AML) arising from MPN

**Interventions**
All patients registered to the interventional component will receive treatment with a minimum of 6 cycles (each cycle 28 days) of 5-azacitidine in combination with one of 5 doses of ruxolitinib (5mg bd, 10mg bd, 15mg bd, 20mg bd, 25mg bd). 5-azacitidine will be administered on days 1-5 and 8-9 of each cycle via subcutaneous injection at a dose of 75mg/m2. Ruxolitinib will be taken orally, twice daily. If patients are achieving a clinical benefit at the end of 6 cycles, they can continue treatment for as long as they are benefitting at the discretion of the Chief Investigator. Patients will be followed up for a minimum of 1 year following registration.
The observational component will receive standard care and the trial will collect information on their outcome.

**Intervention Type**
Drug

### Phase
Phase I

### Drug/device/biological/vaccine name(s)
Ruxolitinib 5-azacitidine

### Primary outcome(s)
To determine the MTD of ruxolitinib in combination with 5-azacitidine; Timepoint(s): Within 1 cycle of treatment

### Key secondary outcome(s))
1. 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% blasts at baseline)
2. International Working Group (IWG) response criteria in myelodysplasia (for patients with <20% blasts at baseline)
3. Change in the proportion of patients who require transfusion of red cells or platelets
4. Achievement of red blood cell (RBC) transfusion independence
5. Achievement of platelet transfusion independence
6. Change in palpable splenomegaly or hepatomegaly
7. Duration of Complete Response (CR) or Partial Response (PR)
8. 12 months Progression-free survival (PFS)
9. 12 months Leukaemia-free survival (LFS)
10. 12 months Overall survival (OS)
11. Duration of treatment
12. Clinical improvement in haemoglobin level
13. Clinical improvement in platelet count
14. Quality of life as measured by the MPN SAF; EQ-5D-5L and EORTC QLQ-C30 (Cycles 1, 2, 4 and 6 for interventional patients; at registration, 3 months and 6 months for observational patients)
15. To determine treatment and outcome of Advanced Phase MPN (MPN-AP) and Blast Phase MPN (MPN-BP) patients who enter the observation component.
16. Change in clonal marker (e.g. JAK2 or CALR allele burden) (to be centrally assessed)

### Completion date
18/08/2022

## Eligibility

### Key inclusion criteria
Current participant inclusion criteria as of 01/08/2018:
For the Interventional component:
1. Age ≥ 16 years old
2. A prior diagnosis of Essential Thrombocythaemia (ET), Polycythaemia Vera (PV) or Myelofibrosis (MF) with one of the following:
2.1. ≥ 10% blasts in blood or bone marrow with or without dysplastic changes (MPN-AP) at baseline
2.2. ≥ 20% blasts in blood or bone marrow (MPN-BP) at baseline
3. In need of treatment in the opinion of the investigator
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-3

5. Adequate liver and renal function, defined as:
5.1. Liver transaminases ≥ 3 × ULN (AST/SGOT and ALT/SGPT)
5.2. Bilirubin <4 x ULN (Patients with elevated bilirubin due to Gilbert's syndrome are eligible)
5.3. GFR ≥ 40 ml/min
6. Willingness to undergo and ability to tolerate assessments during the study including bone marrow assessments and symptom assessments using patient reported outcome instruments
7. Able to give valid informed consent

For the Observational Component
1. Age ≥ 16 years old
2. A prior diagnosis of ET, PV or MF with one of the following:
2.1. Blasts in blood or marrow 10-19%
with or without dysplastic changes (MPN-AP)
2.2 ≥ 20% Blasts (MPN-BP)
2.3. Patients who are unwilling/unable to enter the interventional component and/or fail the interventional component entry criteria. This can include patients entered into studies with more aggressive therapy such as AML 17/19 as well as those receiving palliation only

Previous participant inclusion criteria:
For the Interventional component:
1. Age ≥ 16 years old
2. A prior diagnosis of Essential Thrombocythaemia (ET), Polycythaemia Vera (PV) or Myelofibrosis (MF) with one of the following:
2.1. Blasts in blood or marrow 10-19%
with or without dysplastic changes (MPN-AP)
2.2. ≥ 20% Blasts (MPN-BP)
3. In need of treatment in the opinion of the investigator
4. Eastern Cooperative Oncology Group (ECOG) performance status 0-3
5. Platelet or red blood cell transfusion-dependent
6. Adequate liver and renal function, defined as:
6.1. Liver transaminases ≥ 3 × ULN (AST/SGOT and ALT/SGPT)
6.2. Bilirubin <4 x ULN (Patients with elevated bilirubin due to Gilbert's syndrome are eligible)
6.3. GFR ≥ 40 ml/min
7. Willingness to undergo and ability to tolerate assessments during the study including bone marrow assessments and symptom assessments using patient reported outcome instruments
8. Able to give valid informed consent

For the Observational Component
1. Age ≥ 16 years old
2. A prior diagnosis of ET, PV or MF with one of the following:
2.1. Blasts in blood or marrow 10-19%
with or without dysplastic changes (MPN-AP)
2.2 ≥ 20% Blasts (MPN-BP)
2.3. Patients who are unwilling/unable to enter the interventional component and/or fail the interventional component entry criteria. This can include patients entered into studies with more aggressive therapy such as AML 17/19 as well as those receiving palliation only

## Participant type(s)
Patient

## Healthy volunteers allowed

No

## Age group
Adult

## Lower age limit
18 years

## Sex
All

## Total final enrolment
58

## Key exclusion criteria
Current participant exclusion criteria as of 01/08/2018:
For the Interventional Component:
1. 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
2.New York Heart Association Class II, III, or IV congestive heart failure
3. 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)
4. Erythropoietic agent within 28 days prior to registration
5. Thrombopoietic agent within 14 days prior to registration
6. CYP3A4 inhibitor within 7 days prior to registration
7. Experimental treatment for AML or MPN within 14 days prior to registration (except Ruxolitinib and Hydroxycarbamide which can be taken up until study entry at the prestudy dose. Hydroxycarbamide must be stopped before the first scheduled day of treatment)
8. Previously received 5-azacitidine
9. Known contraindications to receiving azacitidine or ruxolitinib
10. Known HIV seropositivity
11. Known to have active hepatitis A, B, or C
12. Women who are pregnant or lactating. Patients of childbearing potential must have a negative pregnancy test prior to study entry
13. 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.
14. Active infection ≥ grade 3 (CTCAE criteria) at trial entry

For the Observational Component:
No Exclusions planned.

Previous participant exclusion criteria:
For the Interventional Component:
1. 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
2.New York Heart Association Class II, III, or IV congestive heart failure
3. 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

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10. Known HIV seropositivity
11. Known to have active hepatitis A, B, or C
12. Women who are pregnant or lactating. Patients of childbearing potential must have a negative pregnancy test prior to study entry
13. 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.

For the Observational Component:
No Exclusions planned.

### Date of first enrolment
05/01/2016

### Date of final enrolment
30/04/2019

## Locations

### Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

### Study participating centre
### Beatson West of Scotland Cancer Centre
Glasgow
United Kingdom
G12 0YN

### Study participating centre
### Belfast City Hospital
Belfast

United Kingdom
BT9 7AB

**Study participating centre**
**Christie Hospital**
Manchester
United Kingdom
M20 4BX

**Study participating centre**
**Churchill Hospital**
Oxford
United Kingdom
OX3 7LE

**Study participating centre**
**Hammersmith Hospital**
London
United Kingdom
W12 0HS

**Study participating centre**
**Nottingham City Hospital**
Nottingham
United Kingdom
NG5 1PB

**Study participating centre**
**Queen Elizabeth Hospital Birmingham**
Birmingham
United Kingdom
B15 2TH

**Study participating centre**
**Southampton General Hospital**
Southampton
United Kingdom
SO16 6YD

**Study participating centre**
**St James University Hospital**
Leeds
United Kingdom
LS9 7TF

**Study participating centre**
**University Hospital of Wales**
Cardiff
United Kingdom
CF14 4XW

**Study participating centre**
**Bart's and the London Hospital**
London
United Kingdom
EC1A 7BE

**Study participating centre**
**Guy's Hospital**
London
United Kingdom
SE1 7EH

**Study participating centre**
**The Clatterbridge Cancer Centre**
Wirral
United Kingdom
CH63 4JY

**Study participating centre**
**Addenbrooke's Hospital**
Cambridge
United Kingdom
CB2 0QQ

**Study participating centre**

**University College London Hospital**
London
United Kingdom
NW1 2BU

# Sponsor information

**Organisation**
The University of Birmingham (UK)

**ROR**
https://ror.org/03angcq70

# Funder(s)

**Funder type**
Government

**Funder Name**
Bloodwise TAP

# Results and Publications

**Individual participant data (IPD) sharing plan**
The datasets generated during the current study will be available upon request from the CRCTU' s Director's Committee (CRCTU-General@adf.bham.ac.uk) within 6 months after the publication of the outcome measures unless the trial results are to be used as part of a regulatory submission where the release of the data may be delayed or be subject to the approval of a third party. Only scientifically sound proposals from appropriately qualified research groups will be considered for data and/or sample sharing. A data-sharing agreement will cover the terms and conditions of the release of trial data and will include publication requirements, authorship and acknowledgements and obligations for the responsible use of data. An anonymised encrypted dataset will be transferred directly using a secure method and in accordance with the University of Birmingham's IT guidance on the encryption of datasets.

**IPD sharing plan summary**
Available on request

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Basic results | version 1.0 | 17/08/2023 | 17/08/2023 | No | No |

| | | | | | |
|---|---|---|---|---|---|
| HRA research summary | | | 26/07/2023 | No | No |
| Protocol file | version 5.0 | 15/08/2018 | 18/08/2022 | No | No |