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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

EudraCT/CTIS number
2014-002563-16

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
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

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a patient information shee

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

Secondary outcome measures
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)

Overall study start date
05/01/2016

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

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 64; UK Sample Size: 64; Description: As this is a phase I study dose-finding study using a 3+3 cohort design, no formal power calculation has been carried out. A maximum of 24 patients and a minimum of 3 patients will be recruited. Once the MTD has been determined, an additional 10 patients will be recruited to the trial and treated at the MTD to gain further information on the safety and activity of the combined treatment. Up to 30 additional patients will be recruited into an observational component.

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 potassium <3.0 mEq/L, family history of long QT interval syndrome)
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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.

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

England

Northern Ireland

Scotland

United Kingdom

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)

Sponsor details
Haematology Team
Cancer Research UK Clinical Trials Unit
School of Cancer Science
Edgbaston
Birmingham
England
United Kingdom
B15 2TT

Sponsor type
University/education

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
Bloodwise TAP

Results and Publications

Publication and dissemination plan
The results of the trial will be presented at national/international meetings and published in a peer reviewed journal. The primary outcome will be published once all patients have completed one cycle of combination treatment.

Intention to publish date
15/08/2023

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?
Protocol file	version 5.0	15/08/2018	18/08/2022	No	No
HRA research summary			26/07/2023	No	No
Basic results	version 1.0	17/08/2023	17/08/2023	No	No