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Ruxolitinib versus hydroxycarbamide or interferon as first-line therapy in high-risk polcythemia vera

Submission date 20/08/2019	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 28/08/2019	**Overall study status** Ongoing	
Last Edited 06/06/2025	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-ruxolitinib-with-best-available-treatment-for-polycythaemia-vera-mithridate

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2018-001908-11

IRAS number

ClinicalTrials.gov number
NCT04116502

Secondary identifying numbers
RG_16-148; CPMS: 39201

Study information

Scientific Title
A phase III, randomised, open-label, Multicenter International Trial comparing ruxolitinib with either HydRoxycarbamIDe or interferon Alpha as first-line ThErapy for high-risk polycythemia vera (MITHRIDATE)

Acronym
MITHRIDATE

Study objectives
To compare the time to the combined incidence of; major thrombosis, major haemorrhage, death or transformation to MDS, AML or post-PV (PPV) MF in high-risk PV patients randomised to ruxolitinib versus standard care.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/08/2019, London-Fulham Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; Tel: +44 (0)207 104 8235; Email: nrescommittee.london-fulham@nhs.net), REC ref: 19/LO/0951

Study design
Phase III randomised-controlled multi-centre international open-label trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Polycythaemia vera

Interventions
The interventions are Arm A: Ruxolitinib and Arm B: Best Available Therapy (Hydroxycarbamide OR Interferon Alpha, any formulation permitted), which will be selected by the Investigator prior to randomisation. Randomisation will be in a 1:1 ratio and will be performed using a bespoke

computer randomisation system developed by the Cancer Research UK Clinical Trials Unit (CRCTU) employing a stratified minimisation method.
Patients will be stratified by:
1. Country of Origin: UK, France
2. Elected standard of care therapy: IFN, HC
3. Age: <60, ≥ 60
4. Prior thrombosis: No, Yes
5. Length of time from diagnosis: <5: ≥5 years
6. Cardiovascular risk factors, (including the following: arterial hypertension, diabetes, dyslipidemia, tobacco use, obesity): No, Yes

Randomisation will be in a 1:1 ratio AND There will be no cross-over either between arm A and B or between therapies on Arm B.

Arm A: Ruxolitinib – starting dose of 10 mg adjusted in line with the summary product of characteristics throughout for treatment period of 3 years
Arm B: Best Available Therapy (Hydroxycarbamide OR interferon alpha (any formulation permitted)) – treatment for 3 years, dosage is in line with the summary product of characteristics

Patients will be required to attend for study visits to monitor their disease, as they would do whilst following standard care. In addition, patients will be asked to consent to complete quality of life questionnaires every few months and have an additional bone marrow biopsy and an ultrasound scan at 3 years.

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Phase III

Drug/device/biological/vaccine name(s)
Ruxolitinib, hydroxycarbamide, interferon alpha (any formulation permitted)

Primary outcome measure
Event Free Survival (EFS): defined as the time from randomisation to the date of the first event including;
1. Major thrombosis
2. Major haemorrhage
3. Death
4. Transformation to MDS, AML or PPV-MF
Patients who do not experience an event during the trial will be censored at their date last seen

Secondary outcome measures
1. Major thrombosis (both combined and split into venous and arterial)
2. Major haemorrhage
3. Transformation to PPV-MF
4. Transformation to AML and/or MDS
5. Complete haematological response (CHR) as defined by ELN response criteria at 1 year

6. Symptom burden/(QALY) quality of life years gained
7. Health economics including cost-utility and cost-effectiveness analyses
8. Peripheral blood JAK2 V617F allele burden according to ELN response criteria
9. Rates of discontinuation
10. Adverse events
11. Spleen response in patients with splenomegaly at baseline
12. Time free from venesection
13. Rate of second malignancies
14. Change in QRisk score

Overall study start date
16/08/2019

Completion date
30/09/2029

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 06/06/2025:
1. Patient ≥ 18 years of age
2. Diagnosis of PV meeting WHO criteria within the past 15 years
3. Meets criteria of high-risk PV, defined as WBC >11 x 10(9)/l* AND at least ONE of the following:
3.1. Aged >60 years
3.2. Prior thrombosis or major haemorrhage related to disease
3.3. Platelet count >1000 x 10(9)/l*
3.4. Hypertension or diabetes requiring pharmacological therapy
* at any time after diagnosis
4. Patients must have a screening haemoglobin of >8g/dl
5. Patients may have received antiplatelet agents and venesection
6. Patients may have received ONE or less cytoreductive therapy for less than 10 years (BUT they should not be resistant or intolerant to that therapy)
7. Able to provide written informed consent

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Previous participant inclusion criteria as of 09/05/2023:
1. Patient 18 years of age or over
2. Diagnosis of PV meeting WHO criteria within the past 10 years
3. Meets criteria of high-risk PV, defined as WBC >11 x 10(9)/l AND at least ONE of the following:
3.1. Aged >60 years
3.2. Prior thrombosis or major haemorrhage related to disease
3.3. Platelet count >1000 x 10(9)/l at any time after diagnosis
3.4. Diagnosed <10 years
3.5. Received treatment for <5 years
4. Patients may have received antiplatelet agents and venesection
5. Patients may have received ONE or less cytoreductive therapy for less than 5 years (BUT they should not be resistant or intolerant to that
therapy)
6. Able to provide written informed consent

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Previous participant inclusion criteria:
1. Patient 18 years of age or over
2. Diagnosis of PV meeting WHO criteria within the past 10 years
3. Meets criteria of high risk* PV, defined as WBC > 11 x 109/l* AND at least ONE of the following:
3.1. Age > 60 years
3.2. Prior thrombosis or major haemorrhage related to disease
3.3. Platelet count > 1000 x 109/l*
3.4. Diagnosed < 10 years
3.5. Received treatment for < 5 years)
4. Patients may have received antiplatelet agents and venesection
5. Patients may have received ONE or less cytoreductive therapy for less than 5 years (BUT they should not be resistant or intolerant to that
therapy)
6. Able to provide written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 586; UK Sample Size: 293

Key exclusion criteria
Current participant exclusion criteria as of 06/06/2025:
1. Diagnosis of PV > 15 years previously
2. Absence of JAK-2 mutation
3. Patients with any contraindications to any of the investigational medical products
4. Treatment with >1 cytoreductive therapy OR a cytoreductive treatment duration exceeding 10 years OR resistance/intolerance to that therapy
5. Active infection including Human Immunodeficiency Virus (HIV), hepatitis B, hepatitis C, autoimmune hepatitis, tuberculosis
6. Pregnant or lactating patients (Women of childbearing potential must have a negative urine or blood Human Chorionic Gonadotropin pregnancy test prior to trial entry)
7. Patients with lactose allergies, hypersensitivities, or rare hereditary problems, of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
8. Patients with uncontrolled neuropsychiatric disorders
9. Patients with uncontrolled cutaneous cancers
10. Patients and partners not prepared to adopt highly effective contraception measures (if sexually active) whilst on treatment and for at least 6 months after completion of study medication
11. ECOG Performance Status Score ≥ 3

12. Uncontrolled rapid or paroxysmal atrial fibrillation, uncontrolled or unstable angina, recent (within the last 6 months) myocardial infarction or acute coronary syndrome or any clinically significant cardiac disease > NYHA (New York Heart Association) Class II
13. Patients who have transformed to myelofibrosis
14. Previous treatment with ruxolitinib
15. Previous (within the last 12 months) or current platelet count <100 x 109/L or neutrophil count < 1 x 109/L not due to therapy
16. Inadequate liver function as defined by ALT/AST >2.0 x ULN
17. Inadequate renal function as defined by eGFR < 30 mls/min
18. Unable to give informed consent

Additional Exclusion Criteria for France Only:
19. All women of childbearing potential (as per Appendix 8 definition)
20. No affiliation with the French healthcare system
21. Persons under psychiatric care who would impede understanding of informed consent and optimal treatment and follow-up
22. Adults subject to a legal protection measure (guardianship, curatorship and safeguard of justice)
23. Patients deprived of their liberty by a judicial or administrative decision

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Previous participant inclusion criteria:
1. Diagnosis of PV >10 years previously
2. Absence of JAK-2 mutation
3. Patients with any contraindications to any of the investigational medical products
4. Treatment with >1 cytoreductive therapy OR a cytoreductive treatment duration exceeding 5 years OR resistance/intolerance to that therapy
5. Active infection including hepatitis B, hepatitis C, Tuberculosis
6. Pregnant or lactating patients (Women of childbearing potential must have a negative urine or blood Human Chorionic Gonadotropin pregnancy test prior to trial entry)
7. Patients and partners of childbearing potential not prepared to adopt highly effective contraception measures (if sexually active) whilst on treatment and for at least 6 months after completion of study medication
8. ECOG Performance Status Score ≥3
9. Uncontrolled rapid or paroxysmal atrial fibrillation, uncontrolled or unstable angina, recent (within the last 6 months) myocardial infarction or acute coronary syndrome or any clinically significant cardiac disease > NYHA (New York Heart Association) Class II
10. Patients who have transformed to myelofibrosis
11. Previous treatment with ruxolitinib
12. Previous (within the last 12 months) or current platelet count <100 x 109/L or neutrophil count < 1 x 10(9)/L not due to therapy
13. Inadequate liver function as defined by ALT/AST >2.0 x ULN
14. Inadequate renal function as defined by eGFR < 30 ml/min
15. Unable to give informed consent

Date of first enrolment
30/09/2019

Date of final enrolment
30/10/2025

Locations

Countries of recruitment
England

France

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Guys Hospital
Guys Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
Headington
Oxford
United Kingdom
OX3 7LE

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road

Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Royal Bournemouth General Hospital
Castle Lane East
Bournemouth
United Kingdom
BH7 7DW

Study participating centre
Kent and Canturbury Hospital
Ethelbert Road
Canterbury
United Kingdom
CT1 3NG

Study participating centre
Worthing Hospital
Lyndhurst Road
Worthing
United Kingdom
BN11 2DH

Study participating centre
St Richard's Hospital
Spitalfield Lane
Chichester
United Kingdom
PO19 6SE

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

Study participating centre
Royal Gwent Hospital
Cardiff Road
Newport
United Kingdom
NP20 2UB

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Royal Berkshire Hospital
Royal Berkshire Hospital
London Road
Reading
United Kingdom
RG1 5AN

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Gloucestershire Royal Hospital
Great Western Road
Gloucester

United Kingdom
GL1 3NN

Study participating centre
Colchester General Hospital
Colchester District General Hosp.
Charter Way
Turner Road
Colchester
United Kingdom
CO4 5JL

Study participating centre
Huddersfield Royal Infirmary
Acre Street
Huddersfield
United Kingdom
HD3 3EA

Study participating centre
Calderdale Royal Hospital Pts Control
The Calderdale Royal Hospital
Godfrey Road
Salterhebble
Halifax
United Kingdom
HX3 0PW

Study participating centre
Castle Hill Hospital
Entrance 3
Castle Road
Cottingham
United Kingdom
HU16 5JQ

Study participating centre
Warwick Hospital
Lakin Road

Warwick
United Kingdom
CV34 5BW

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
Lothian
United Kingdom
EH4 2XU

Study participating centre
St John's Hospital
Howden West
Livingston
Lothian
United Kingdom
EH54 6PP

Study participating centre
Raigmore Hospital
Old Perth Rd
Inverness
United Kingdom
IV2 3UJ

Study participating centre
University College Hospital Elizabeth Garrett Anderson Wing
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Arrow Park Hospital
Arrowe Park Hospital
Arrowe Park Road
Wirral
United Kingdom
CH49 5PE

Study participating centre
St George's Hospital
Blackshaw Road
Tooting
London
United Kingdom
SW17 0QT

Study participating centre
Birmingham Heartlands Hospital
Bordesley Green East
Bordesley Green
Birmingham
United Kingdom
B9 5SS

Study participating centre
Good Hope Hospital
Rectory Road
Sutton Coldfield
United Kingdom
B75 7RR

Study participating centre

Freeman Road Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Royal Cornwall Hospital (treliske)
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre
Blackpool Victoria Hospital
Whinney Heys Road
Blackpool
United Kingdom
FY3 8NR

Study participating centre
Southampton
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Northampton
Northampton General Hospital
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre
Wexham Park Hospital
Wexham Street
Wexham

Slough
United Kingdom
SL2 4HL

Study participating centre
Royal United Hospital
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
The James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Northumbria Healthcare NHS Foundation Trust
North Tyneside General Hospital
Rake Lane
North Shields
United Kingdom
NE29 8NH

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Belfast City Hospital
51 Lisburn Rd
Belfast
United Kingdom
BT9 7AB

Study participating centre
Kettering General Hospital
Rothwell Road
Kettering
United Kingdom
NN16 8UZ

Study participating centre
Halton General Hospital
Hospital Way
Halton
Runcorn
United Kingdom
WA7 2DA

Study participating centre
New Cross Hospital
Wolverhampton Road
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
Russells Hall Hospital
Pensnett Road
Dudley
United Kingdom
DY1 2HQ

Study participating centre

Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Study participating centre
Derriford Hospital
Derriford Road
Crownhill
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
York Hospital
Wigginton Road
York
United Kingdom
YO31 8HE

Sponsor information

Organisation
University of Birmingham

Sponsor details
Edgbaston
Birmingham
England
United Kingdom

B15 2TT
+44 (0)121 414 3792
mithridate@trials.bham.ac.uk

Sponsor type
University/education

Website
http://www.birmingham.ac.uk/

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Industry

Funder Name
Novartis

Alternative Name(s)
Novartis AG, Novartis International AG

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Funder Name
MPN Voice

Results and Publications

Publication and dissemination plan
There will be a trial website (currently under construction so URL unavailable) that will include the protocol, patient documents etc. for sites to download.
Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham.
Intellectual property rights will be addressed in the corresponding contracts between Sponsor and national coordinating centres/sites.
Individual countries will be allowed to publish their efficacy results, however, the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the TMG decides otherwise.

Intention to publish date
30/09/2029

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Claire Harrison (Claire.Harrison@gstt.nhs.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No