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Clinical trial for patients with TKI resistant chronic myeloid leukaemia in chronic or accelerated phase

Submission date 22/01/2019	**Recruitment status** Stopped	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 13/02/2019	**Overall study status** Stopped	
Last Edited 06/11/2023	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-targeted-drugs-for-chronic-myeloid-leukaemia-when-treatment-has-stopped-working-taster

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-001843-29

Protocol serial number
TASTER2018

Study information

Scientific Title
An umbrella adaptive randomised multi–arm screening phase II trial for patients with 2nd/3rd generation TKI resistant chronic myeloid leukaemia

Acronym
TASTER (TArgeting STEm cell Resistance)

Study objectives
The trial will investigate whether a novel agent can be combined with TKI to improve treatment response, as measured by BCR-ABL1IS transcript levels in chronic and accelerated phase chronic myeloid leukaemia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/05/2019, London – City & East Research Ethics Committee (Bristol Research Ethics Committee Centre, Whitefriars, Level 3, Block B, Lewins Mead, Bristol, BS1 2NT, UK; Tel: +44 (0) 207 104 8171; Email: nrescommittee.london-cityandeast@nhs.net), ref: 19/LO/0529

Study design
Adaptive randomised screening phase II design

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic myeloid leukaemia

Interventions
The trial will commence initially with a control arm (TKI) and 2 experimental arms (TKI + EZH2i [Tazemetostat-EPZ-6438], TKI + MDM2i [Idasanutlin –RO5503781]). The number of experimental arms will change over time as further novel agents are introduced to the trial via amendment. Patients will be randomised 1:1:1 to a control arm and 2 experimental arms.

Arm A: TKI monotherapy (control arm):
Patients will continue on the same TKI they have been taking for previous 3 (accelerated phase) and 6 (chronic phase) months prior to entering the trial continuously for each cycle e.g. day 1 -28. Authorised TKIs are imatinib, nilotinib, dasatinib, bosutinib and ponatinib.

Arm B: EPZ-6438 - Tazemetostat with TKI:
Dose level -1 – low dose oral 400 mg BD 28 days continuous
Dose level 1 – starting dose oral 600 mg BD 28 days continuous
Dose level 2 – escalation dose oral 800 mg BD 28 days continuous
Authorised TKIs are imatinib, nilotinib, dasatinib, bosutinib and ponatinib

Patients will continue on the same TKI they have been taking for previous 3 (accelerated phase) or 6 (chronic phase) months prior to entering the trial. The TKI will be taken in combination with Tazemetostat. Note the TKI is taken continuously throughout each cycle e.g. days 1-28

Arm C: RO5503781 - Idasanutlin with TKI:
Dose level -1 – low dose oral idasanutlin (Spray Dried Powder [SDP] DP formulation) 100 mg OD for days 1-5 of 28 day cycle
Dose level 1 – starting dose oral idasanutlin (Spray Dried Powder [SDP] DP formulation) SDP 150 mg OD for days 1-5 of 28 day cycle
Dose level 2 – escalation dose oral idasanutlin (Spray Dried Powder [SDP] DP formulation) SDP 200 mg OD for days 1-5 of 28 day cycle
Authorised TKIs are imatinib, nilotinib, dasatinib, bosutinib and ponatinib
Patients will continue on the same TKI they have been taking for previous 3 (accelerated phase) or 6 (chronic phase) months prior to entering the trial. The TKI will be taken in combination with Idasanutlin. Note the TKI is taken continuously throughout each cycle e.g. days 1-28

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Imatinib, Nilotinib, Dasatinib, Bosutinib, Ponatinib, Tazemetostat, Idasanutlin

Primary outcome(s)
The proportion of treatment 'responders' defined as patients who achieve a > 0.5 log reduction in BCR-ABL1 mRNA levels at any time during 32 weeks of treatment (by 33 weeks from baseline)

Key secondary outcome(s))
1. Toxicities assessed according to NCI CTCAE V5.0
2. Durability of improvement in BCR-ABL1 mRNA level in responding chronic and accelerated phase CML patients, measured by levels of BCR ABL1 every 3 months from baseline until end of study
3. Rate of haematological improvement measured by standard FBC and manual differential WBC assessed monthly from baseline to 32 weeks
4. Rate of CyR improvement by 32 weeks, measured by standard cytogenetics - metaphase cytogenetics on >20 metaphases obtained from WBC in bone marrow
5. Rate of molecular improvement by 32 weeks (BCR-ABL<10%, < 1%, < 0.1%, and , 0.01%), measured by levels of BCR ABL1 assessed every 3 months from baseline until end of study
6. Drug-drug interactions by measuring levels of TKI and novel agents (i.e. PK) at specified timepoints during cycles 1 and 2 on experimental arms of the study
7. Overall patient survival, event-free survival and relapse-free survival will be determined by the time from baseline (randomisation) to each of death, event and relapse. The comparisons between each experimental arm and the control arm will be made using a Cox regression model. Event Free Survival (EFS) will be defined as follows: (Date of event - start date of study medication). For the purposes of the study an 'event' will be defined as the first occurrence of one of the following:
7.1. Death from any cause
7.2. Disease progression (as defined below)
7.3. Loss of CHR defined as the appearance of any of the following, confirmed by a second

determination ≥ 1 month later: WBC count that rises to > 20.0 x 109/L, platelet count that rises to ≥ 600 x 109/L, appearance of blasts in the peripheral blood
7.4. Increasing WBC count: for patients not achieving a CHR, haematological progression will be defined as a doubling of WBC count at least one month apart with at least the second value >20. 0 x 109/L
7.5. Loss of major cytogenetic response (MCR): for patients that were in MCR at study entry; loss of MCR will be defined as an increase in the Ph+ bone marrow cells by at least 30 percentage points (e.g., from 20% to 50%, or from 30% to 60%) confirmed by a second cytogenetic analysis ≥1 month later
8. Time to haematological, cytogenetic and molecular response will be determined by the time from baseline (randomisation) to each of haematological, cytogenetic and molecular response.
9. Time to molecular, cytogenetic or haematological relapse and to progression to accelerated or blast phase and to progression to accelerated or blast phase will be determined by the time from baseline (randomisation) to each of molecular, cytogenetic or haematological relapse, and progression.
10. Quality of life measured using MDASI-CML and EQ5D at baseline, C9 D1, C16 D1 and C20 D1

Completion date
28/02/2025

Reason abandoned (if study stopped)
Lack of funding/sponsorship

Eligibility

Key inclusion criteria
Inclusion Criteria – Chronic Phase Patients:
1. Patient aged >18 years
2. Patient has given written informed consent to participate in the trial
3. Patients with Ph+, BCR ABL + Chronic Phase CML
4. Prior treatment with at least two 2nd (nilotinib, dasatinib or bosutinib) or 3rd generation (ponatinib) TKI, or imatinib after failure or intolerance to 2nd/3rd generation TKI, on same TKI for period of > 6 months
5. No switch between TKIs within the last 6 months
6. ELN failure defined as BCR-ABL level on IS of >10% and/or Ph >35% at > 6 months of taking 2nd or subsequent line of TKI therapy or >1% and/or Ph >0% by 12 months of taking 2nd or subsequent line of TKI therapy. Patients entering TASTER on imatinib need to meet the above definition for failure of 2nd or subsequent line of TKI therapy and/or be intolerant to 2nd or subsequent line of TKI therapy, and have ELN failure on imatinib
7. Patients with ECOG grade 0 to 2
8. Patients require tohave adequate renal function defined as calculated creatinine clearance > 40ml/min per the Cockcroft and Gault formula (appendix 5) or local institutional standard formula
9. Adequate haematological and biochemical function as indicated below. These measurements must be performed within 7 days prior to randomisation:
9.1. ALT or AST < 2.5 x ULN
9.2. Total Bilirubin < 1.5 x ULN (for patients with bilirubin >1.5 x ULN, they will require to have conjugated and unconjugated bilirubin checked, if conjugated bilirubin < 1.5 x ULN the patient will be eligible)
9.3. Lipase or amylase < 1.5 x ULN
9.4. Neutrophils > 1.0 x 109/l

9.5. Platelets > 100 x 109/l
9.6. WBC < 50 x 109/l
10. Willingness to comply with scheduled visits, treatment plans and laboratory tests and other trial procedures
11. Ability to swallow oral medications
12. Females of childbearing potential must have a negative pregnancy test within 7 days prior to randomisation and agree to use highly effective contraceptive measures (see section 7.1.8.1) from the time of negative pregnancy test up to 90 days after the last dose of study drug. Non-childbearing potential must be evidenced by fulfilling one of the following criteria at screening:
12.1. Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
12.2. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
13. Male patients with partners of child-bearing potential must agree to use highly effective contraceptive measures for the duration of the study and up to 90 days after the last dose of study drug

Inclusion Criteria – Accelerated Phase Patients:
1. Patient aged >18 years
2. Patient has given written informed consent to participate in the trial.
3. Patients with Ph+, BCR-ABL + Accelerated Phase CML defined as presence of one of the following:
3.1. Blasts in blood or marrow 15-29%, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30%
3.2. Basophils in blood ≥20%
3.3. Persistent thrombocytopenia (<100x109/L) unrelated to therapy
3.4. Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment
4. Treatment with > one 2nd (nilotinib, dasatinib or bosutinib) or 3rd generation (ponatinib) TKI, or imatinib after failure or intolerance to 2nd/3rd generation TKI, on same TKI for period of > 3 months
5. No switch between TKIs within the last 3 months
6. ELN failure in accelerated phase defined as BCR-ABL level on IS of >10% and/or Ph>65% at 3 months or >10% or Ph >35% at > 6 months or >1% and/or Ph >0% by 12 months of taking 2nd or subsequent line of TKI therapy Patients entering TASTER on imatinib need to meet the above definition for failure of 2nd or subsequent line of TKI therapy and/or be intolerant to 2nd or subsequent line of TKI therapy and have ELN failure on imatinib
7. Patients with ECOG grade 0 to 2
8. Patients require to have adequate renal function defined as calculated creatinine clearance > 40ml/min per the Cockcroft and Gault formula (appendix 5) or local institutional standard formula
9. Adequate haematological and biochemical function as indicated below. These measurements must be performed within 7 days prior to randomisation:
9.1. ALT or AST < 2.5 x ULN
9.2. Total Bilirubin < 1.5 x ULN (for patients with bilirubin > 1.5 x ULN they will require to have conjugated and unconjugated bilirubin checked, if conjugated bilirubin < 1.5 x ULN the patient will be eligible)
9.3. Lipase or amylase < 1.5 x ULN
9.4. Neutrophils > 1.0 x 109/l
9.5. Platelets > 100 x 109/l
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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Exclusion Criteria – Chronic Phase Patients:
1. Pregnant or lactating women
2. Females of child bearing potential or males not willing to use a highly effective method of contraception
3. Patient in planning for allogeneic SCT within 6 months
4. Patients with cardiovascular disease defined as:
4.1. QTc > 450 (males), >470 (females)
4.2. Stage II to IV congestive heart failure (CHF) as determined by the New York Heart Association (NYHA) classification system for heart failure within the previous 6 months
4.3. Myocardial infarction within the previous 6 months
4.4. Symptomatic cardiac arrhythmia requiring treatment within the previous 6 months
4.5. Grade III or IV fluid retention within the previous 6 months
5. Known BCR-ABL kinase domain mutation expected to be sensitive to an alternative TKI
6. Patients with a history of another malignancy other than non-metastatic basal cell or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix; the exception is if patients have been disease-free for at least 5 years, and are deemed by the investigator to be low risk for recurrence of that malignancy. Patients with a history of breast cancer continuing on tamoxifen or an aromatase inhibitor are eligible for the study if they have been disease free for at least 5 years
7. Patients with history of T-cell lymphoblastic lymphoma (T-LBL) or T-cell acute lymphoblastic leukaemia (T –ALL)
8. Patients with thrombocytopenia, neutropenia or anaemia of grade > 3 (per CTCAE version 5.0

criteria) or any prior history of other myeloid malignancies including myelodysplastic syndrome (MDS)
9. Patients taking medications that are known strong CYP3A4 inducers (including St John's Wort) and strong CYP3A4 inhibitors unless stopped at least 14 days before commencing trial medication. Moderate CYP3A4 inducers and inhibitors should be used with caution
10. Patients taking medications that are known strong CYP2C8 inhibitors and inducers or CYP2C8 substrates unless stopped at least 14 days before commencing trial medications. Moderate CYP2C8 inducers and inhibitors may be used with caution
11. Patients taking medications that are known UGT inhibitors and inducers unless stopped at least 14 days before commencing trial medications
12. Patients taking medications that are OATP1B1 and OATP1B3 substrates with a narrow safety window (or safety concerns) should be stopped at least 14 days before commencing trial medications. Others should be used with caution
13. Patients taking concomitant treatment with medicines listed as prohibited in section 5.3.9 for imatinib, section 5.4.8 nilotinib, section 5.5.8 dasatinib, section 5.6.8 bosutinib or section 5.7.8 ponatinib (as applicable to patient)
14. Patients unable to temporarily interrupt treatment with oral or parental anticoagulants/anti platelet agents (e.g. warfarin, chronic daily treatment with aspirin [>325 mg/day], clopidrogel, dabigatran, apixiban, rivaroxaban, or subcutaneous [SC] anticoagulant prophylaxis) during treatment phase. These agents must be stopped at least 7 days (or 5 half lifes) before commencing trial medications
15. Patients unwilling to remove Seville oranges, grapefruit juice and grapefruits from their diet
16. Patients that have received any systemic anti-cancer therapy (except hydroxycarbamide, anagrelide, low dose arabinosyl-cytarabine (LDAC), steroids, or interferon), surgery or radiotherapy within the 28 days prior to randomisation
17. Treatment with any other investigational agent within 14 days prior to first dose of medication on TASTER trial
18. History of physical or psychiatric disorder that would prevent informed consent and compliance with protocol
19. Patients with acute infections
20. Patients which have had a cerebrovascular accident within 6 months prior to randomisation
21. Patients with active GI conditions (e.g. Grade > 2 graft-versus-host-disease) and uncontrolled irritable bowel disease (i.e. Crohn's disease, ulcerative colitis, diverticulosis-associated colitis and Behcet's disease)
22. Patients with any other severe concurrent disease which may increase the risk associated with trial participation or trial treatment
23. Any psychological, familial, sociological or geographical consideration potentially hampering compliance with trial protocol and follow-up schedule
24. Patients known to have a positive Hepatitis B serology
25. Patients with a history of previous therapy with tazemetostat or idasanutlin at any time
26. Patients with a history of previous therapy with EZH2 inhibitor
27. Patients with a known hypersensitivity to imatinib, nilotinib, dasatinib, bosutinib, ponatinib, idasanutlin or tazemetostat or any of their excipients
28. Patients with rare hereditary problems of galactose intolerance or the Lapp lactase deficiency or glucose-galactose malabsorption

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14. Patients unable to temporarily interrupt treatment with oral or parental anticoagulants/anti platelet agents (e.g. warfarin, chronic daily treatment with aspirin [>325 mg/day], clopidrogel, dabigatran, apixiban, rivaroxaban, or subcutaneous [SC] anticoagulant prophylaxis) during treatment phase. These agents must be stopped at least 7 days (or 5 half lifes) before commencing trial medications
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20. Patients which have had a cerebrovascular accident within 6 months prior to randomisation
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28. Patients with rare hereditary problems of galactose intolerance or the Lapp lactase deficiency or glucose-galactose malabsorption

Date of first enrolment
28/08/2019

Date of final enrolment
28/02/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
NHS Greater Glasgow and Clyde
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 OYN

Study participating centre
IMPERIAL COLLEGE HEALTHCARE NHS TRUST
Hammersmith Hospital
Du Cane Road
London
United Kingdom
W12 OHS

Study participating centre
OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST
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Study participating centre
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University Hospitals of Leicester
Leicester Royal Infirmary
Leicester
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LE1 5WW

Study participating centre
Leeds Teaching Hospital NHS TRUST
St James's University Hospital
Beckett Street
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LS9 7TF

Study participating centre
The Newcastle Upon Tyne Hospitals
Freeman Hospital
Freeman Road

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United Kingdom
NE7 7DN

Study participating centre
ROYAL LIVERPOOL AND BROADGREEN UNIVERSITY HOSPITALS NHS TRUST
ROYAL LIVERPOOL UNIVERSITY HOSPITAL
PRESCOT STREET
Liverpool
United Kingdom
L7 8XP

Study participating centre
KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST
Kings College Hospital
Denmark Hill
London
United Kingdom
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Study participating centre
NHS Lothian
Western General Hospital
Crewe Road
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EH4 2XU

Study participating centre
SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST
NORTHERN GENERAL HOSPITAL
HERRIES ROAD
SHEFFIELD
United Kingdom
S5 7AU

Sponsor information

Organisation

NHS Greater Glasgow and Clyde

Organisation
University of Glasgow

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The CTU is committed to furthering cancer research by sharing de-identified individual-patient data (IPD) from its studies with others in the field who wish to use the data for high quality science. They are happy to consider proposals from researchers and will share IPD to the maximum extent, subject to individual study constraints relating to:-
1. Ethical approval and informed consent
2. Contractual and legal obligations
3. Publication timelines (data will not normally be shared prior to the publication of the primary results)
In addition, all proposals will be reviewed for their scientific merit by the CTU and the study Chief Investigator. Only data relevant to the objectives of a particular proposal will be provided. An independent review process will be undertaken in cases of disagreement between the applicant and the CTU/Chief Investigator.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No