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A Phase Ib study of eltrombopag and azacitidine in patients with high risk myelodysplastic syndromes and related disorders

Submission date 05/07/2013	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 05/07/2013	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 21/07/2022	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/trials/trials-search/a-trial-eltrombopag-azacitidine-myelodysplastic-syndrome-elastic

Contact information

Type(s)
Scientific

Contact name
Mrs Becky Bishop

Contact details
Centre for Clinical Haematology
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH
+44 (0) 121 371 7868
elastic@trials.bham.ac.uk

Additional identifiers

EudraCT/CTIS number
2013-000341-39

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
14761

Study information

Scientific Title
A Phase Ib study of eltrombopag and azacitidine in patients with high risk myelodysplastic syndromes and related disorders

Acronym
ELASTIC

Study objectives
ELASTIC is a 3+3 cohort trial designed to evaluate the Maximum Tolerated Dose (MTD) and Optimal Biological Dose (OBD) of eltrombopag in combination with azacitidine. This trial will recruit patients with IPSS INT-2/high-risk Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukaemia (CMML-2) and Acute Myeloid Leukaemia (AML) with less than 30% blasts.
The objectives of the trial are to evaluate the safety and tolerability of the oral thrombopoietin receptor agonist eltrombopag in combination with azacitidine in patients with advanced MDS and establish the Maximum Tolerated Dose (MTD) and Optimum Biological Dose (OBD).
The trial will also aim to investigate the effect of eltrombopag with azacitidine on the fate of MDS/AML stem cell progenitors from patients so treated. The feasibility of Leukaemic Stem Cell (LSC) tracking as a marker of response and predictor of treatment failure in future Phase II/III studies will be explored.
A maximum of 27 patients will be recruited to the 3+3 dose finding component of the study and a minimum of 3. The number of patients recruited is determined by the maximum dose of 300mg.
An additional 10 patients will then be recruited at the MTD to allow a preliminary estimate of activity.
A maximum of 37 patients in total will be recruited to this study.

Ethics approval required
Old ethics approval format

Ethics approval(s)
13/SC/0309; First MREC approval date 28/06/2013

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

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)

Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Topic: National Cancer Research Network; Subtopic: Haematological Oncology; Disease: Miscellaneous

Interventions
Azacitidine, Hypomethylating agent used within its licensed indication; Eltrombopag, Thrombopoietin receptor (TpoR) agonist; Follow Up Length: 7 month(s); Study Entry : Registration only

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Eltrombopag, azacitidine

Primary outcome measure
Safety and tolerability of eltrombopag in combination with azacitidine; Timepoint(s): Within 5 weeks (1 cycle) of azacitidine treatment

Secondary outcome measures
1. To establish the Optimal Biological dose (OBD) of eltrombopag in combination with azacitidine; Timepoint(s): Within 5 weeks (1 cycle) of azacitidine treatment
2. To evaluate evidence for a dose response effect of eltrombopag on bone marrow blast percentage; Timepoint(s): During 3 cycles of azacitidine treatment
3. To evaluate the activity of eltrombopag plus azacitidine per IWG 2006 response criteria for MDS; Timepoint(s): During 3 cycles of azacitidine treatment
4. To evaluate the dosage effect of eltrombopag on stem/progenitor subset numbers and fate; Timepoint(s): During 3 cycles of azacitidine treatment
5. To evaluate the effect of eltrombopag on azacitidine treatment delays and dose reductions; Timepoint(s): During 3 cycles of azacitidine treatment
6. To evaluate the effect of eltrombopag on bleeding complications; Timepoint(s): During 3 cycles of azacitidine treatment
7. To evaluate the effect of eltrombopag on platelet counts; Timepoint(s): During 3 cycles of azacitidine treatment
8. To evaluate the effect of eltrombopag on the need for platelet transfusions; Timepoint(s): During 3 cycles of azacitidine treatment

Overall study start date
02/09/2013

Completion date
31/08/2020

Eligibility

Key inclusion criteria
1. Age >=16 years of age
2. Platelet count at baseline <150 x 109/l
3. Myelodysplastic Syndromes (MDS) classified as Intermediate 2 risk or high risk according to the International Prognostic Scoring System (IPSS) at registration or Chronic Myelomonocytic Leukaemia (CMML) with 10-29% bone marrow blasts without proliferation (peripheral white blood cell count <13 x 109/l) or Acute Myeloid Leukaemia (AML) with 20-30% bone marrow blast
4. Subjects must have platelet count and platelet transfusion data available over a period of 4 weeks prior to registration
5. A baseline bone marrow examination to evaluate blast percentage, karyotype and assessment of fibrotic change within 8 weeks of registraton
6. Alanine Aminotransferase ALT/Aspartate Aminotransferase (AST) < 3 x upper limit of normal ECOG = 2
7. Valid informed consent
Target Gender: Male & Female ; Lower Age Limit 16 years

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 37; UK Sample Size: 37; Description: As this is a 3+3 design, no formal power calculation has been carried out and analysis will be descriptive only.

Total final enrolment
31

Key exclusion criteria
1. AML with >30% blasts
2. Known HIV positive
3. Known liver cirrhosis
4. Uncontrolled infection (grade 4 CTCAE v4)
5. Previous exposure to azacitidine
6. Previous exposure to thrombomimetic agents
7. Use of prior investigational agents within 6 weeks
8. Other severe, concurrent diseases or mental disorders
9. Concurrent active or previous malignancy within the last 3 years except controlled, localised prostate cancer on hormone therapy or non-melanoma skin malignancy or cervical carcinoma in situ or completely resected colonic polyps carcinoma in situ
10. Bone marrow fibrosis

11. Clinical evidence of splenomegaly
12. Known hypersensitivity to study drugs or any of their excipients
13. Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry)
14. Females of childbearing potential (i.e. not postmenopausal
or surgically sterilised) who are not willing to use adequate methods of contraception to prevent pregnancy or abstain from heterosexual activity for the duration of the trial and for at least 3 months following treatment discontinuation.
15. Male patients who are not willing to use an adequate method of contraception for the duration of the trial treatment if engaged in sexual activity with a female of childbearing potential and for at least 3 months following treatment discontinuation
16. Patients of east Asian ancestry*
* Patients will be excluded if either parent is East Asian (such as Chinese, Japanese, Taiwanese or Korean). In previous studies, the pharmacokinetics of eltrombopag in patients of East Asian ancestry differs significantly from the non-East Asian patients. The SPC for eltrombopag recommends patients receive 50% of the recommended dose. As this is a dose finding study, inclusion of these patients may impair an accurate finding of MTD and OBD that could be applied to the UK population.

Date of first enrolment
02/09/2013

Date of final enrolment
05/10/2015

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Birmingham
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
University of Birmingham

Sponsor details
Edgbaston
Birmingham

England
United Kingdom
B15 2TT

Sponsor type
University/education

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Leukaemia and Lymphoma Research

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed journal. Currently under review.

Intention to publish date
01/08/2022

Individual participant data (IPD) sharing plan
The Cancer Research UK Clinical Trials Unit (CRCTU) is committed to responsible and controlled sharing of anonymised clinical trial data with the wider research community to maximise potential patient benefit while protecting the privacy and confidentiality of study participants. A summary of the clinical trial results is already available.
Participant data and the associated supporting documentation will typically be available for all CRCTU clinical trials within 6 months after the publication of the outcome measures. Only scientifically sound proposals from appropriately qualified research groups will be considered

for data sharing. Data Sharing Requests will be reviewed independently by the CRCTU Directors in discussion with the Chief Investigator and relevant Trial Management Group and due diligence checks will be performed.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		23/09/2021	20/05/2022	No	No
Plain English results	Cancer Research UK summary of results		21/07/2022	No	Yes
HRA research summary			28/06/2023	No	No