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De-escalation and stopping treatment of imatinib, nilotinib or sprycel in chronic myeloid leukaemia

Submission date 12/06/2013	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 12/06/2013	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 06/06/2017	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol

Background and study aims
The aim of this study is to investigate whether some patients, with excellent responses to treatment of white blood cell cancer [chronic myeloid leukaemia (CML)], are being over-treated and can remain well on either a lower dose of treatment or without treatment at all. The dose of drugs, imatinib (Glivec), nilotinib (Tasigna) or dasatinib (Sprycel), will initially be cut to half the standard dose for 12 months and then treatment will be stopped completely for a further two years. This study will also help to develop a treatment decrease and stopping strategy for future patients.

Who can participate?
Patients who have been treated with imatinib, dasatinib or nilotinib for at least 3 years from original diagnosis and whose BCR-ABL1 levels (measure of a gene fusion product) have been at or below 0.1% on all tests for the past 12 months.

What does the study involve?
Two groups are studied: those in whom BCR-ABL1 has been undetectable for at least 12 months in at least three samples (molecular remission at the 4-log level, abbreviated as the MR4 group) and those in whom BCR-ABL1 is detectable on some or all tests in the past 12 months, but always below a level of 0.1% (major molecular response, abbreviated to the MMR group). Both groups are treated identically though analysed separately, by initially decreasing treatment to half of the standard dose for 12 months. If the BCR-ABL1 level remains at or below 0.1%, treatment is then completely stopped and observation continues for a further 24 months.

What are the possible benefits and risks of participating?
It is estimated that DESTINY will bring substantial savings to the NHS. Dose decrease or discontinuation of treatment might improve quality of life. Imatinib has several mild but persistent side effects such as rash, oedema and stomach upset. Similarly, dasatinib may cause fluid accumulation in lungs and hypertension and nilotinib may be associated with an increased late risk heart diseases.

Where is the study run from?
1. The Royal Liverpool University Hospital (UK) (lead centre)
2. Cancer Research UK Liverpool Cancer Trials Unit (UK) (coordinating centre)

When is study starting and how long is it expected to run for?
August 2013 to August 2014

Who is funding the study?
Leukaemia & Lymphoma Research (UK)

Who is the main contact?
Tony Coffey
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Study website
http://www.lctu.org.uk/trial/trial_info.asp?id=101&tgcode=5&menuid=30

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2012-004025-24

IRAS number

ClinicalTrials.gov number
NCT01804985

Secondary identifying numbers
14492

Study information

Scientific Title

A trial of de-escalation and stopping treatment in chronic myeloid leukaemia patients with excellent responses to tyrosine kinase inhibitor therapy (De-Escalation and Stopping Treatment of Imatinib, Nilotinib or sprYcel in chronic myeloid leukaemia) (DESTINY)

Acronym
DESTINY

Study objectives
The DESTINY trial will evaluate the feasibility of de-escalation and then stopping treatment in chronic myeloid leukaemia patients with excellent responses to prior treatment. DESTINY is conceived as a pilot for including this strategy in the next phase III study for the UK (to be known as SPIRIT3). Patients are eligible if in first chronic phase; have been treated with imatinib, dasatinib or nilotinib for at least 3 years from original diagnosis; and whose BCR-ABL1 levels have been at or below 0.1% on all tests for the past 12 months. Two groups will be studied; those in whom BCR-ABL1 has been undetectable for at least 12 months in at least 3 samples, all of which have at least 104 control transcripts (molecular remission at the 4-log level, abbreviated as the MR4 group), and those in whom BCR-ABL1 is detectable on some or all tests in the past 12 months, but always below a level of 0.1% (major molecular response, abbreviated to the MMR group). Both MR4 and MMR groups will be treated identically though analysed separately, by initially de-escalating treatment to 50% of the standard dose for 12 months. If the BCR-ABL1 level remains at or below 0.1%, treatment is then completely stopped, and observation continues for a further 24 months.

The objective of DESTINY is to determine the safety and efficacy of initially de-escalating and then stopping tyrosine-kinase inhibitor (TKI) treatment, in CML patients with either undetectable disease or with stable MMR.

Ethics approval required
Old ethics approval format

Ethics approval(s)
13/NW/0265; First MREC approval date 20/05/2013

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: Leukaemia (chronic)

Interventions
Dasatinib, imatinib or nilotinib; de-escalated to half the standard dose for 12 months. If on imatinib, the dose should be decreased to 200mg daily, if on nilotinib, to 200mg twice daily (which is half the standard dose for second line use, since it is anticipated that the vast majority of nilotinib entrants will be receiving 400mg twice daily because of prior imatinib intolerance) and if on dasatinib then to 50 mg daily. Follow Up Length: 37 month(s).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Imatinib, nilotinib, dasatinib

Primary outcome measure
Proportion of patients who can de-escalate and stop TKI without losing MMR. Timepoint(s): The proportion of patients who can first de-escalate their treatment (to half the standard dose)

Secondary outcome measures
1. Lab studies to define subsets of patients who are more likely to relapse on de-escalation /cessation; Timepoint(s): End of follow-up
2. Proportion of patients who can de-escalate but lose MMR on TKI cessation; Timepoint(s)
3. Proportion of patients who can successfully de-escalate their treatment (to half the standard dose o; Proportion of patients who lose MMR on de-escalation/stopping TKI but regain MMR on TKI resumption; Timepoint(s):
4. Proportion of patients who lose their MMR on de-escalation/stopping and regain MMR on resumption of Quality of Life; Timepoint(s): Baseline 1, 2, 3, 6, 9, 12, 13, 14, 16, 19, 22, 25, 29, 33 and 37 months after trial entry

Overall study start date
01/08/2013

Completion date
01/08/2014

Eligibility

Key inclusion criteria
1. CML in first chronic phase
2. Demonstration of BCR-ABL1 positivity at or shortly after original diagnosis*
3. Written informed consent
4. Must have received TKI treatment for at least 3 years
5. At least 3 molecular results over the preceding 12 months, that fit either of the following groups (results from any UK lab are acceptable):

5.1. (MR4 group) all the available BCR-ABL1 molecular results over the preceding 12 months are in MR4 (MR4 is defined as a BCRABL1/ABL1 ratio of zero, with at least 10,000 ABL1 control transcripts)
5.2. (MMR group) some or all BCR-ABL1 molecular results are in MMR (BCRABL1/ ABL1 ratio of 0.1% or less, but not zero, with at least 10,000 ABL1 control transcripts). If the results over the preceding 12 months are a mix of MMR and undetectable BCR-ABL1, then the patient is eligible for the MMR but not the MR4 group.
*Patients who are Philadelphia chromosome (Ph) negative (or whose Ph status is not known) are eligible. Patients who do not have a standard BCR-ABL1 fusion transcript (i.e. other than e13a2 or e14a2, also known as b2a2 and b3a2) are eligible, but before screening the patient, contact should be made with Prof Foroni at Imperial College (see contacts) since specialised quantitative molecular assessment will be required.
Target Gender: Male & Female; Lower Age Limit 18 years

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 168; UK Sample Size: 168; Description: 84 patients will be recruited from both the 'MR4' and 'MMR' groups of patients.

Key exclusion criteria
1. Age under 18
2. Life expectancy is predicted to be less than 37 months because of intercurrent illness
3. Presence of serious concomitant illness (e.g. heart, renal, respiratory or active malignant disease) that might preclude completion of the study
4. CML in accelerated phase or blast crisis at any time
5. Any molecular result during the preceding 12 months that is not in either MMR or MR4
6. Treatment with higher than standard TKI doses (standard is defined as imatinib 400mg daily, nilotinib 400mg twice daily or dasatinib 100mg daily)
7. Patients who switched previous licensed TKI treatment (imatinib, nilotinib or dasatinib) twice or more because of intolerance
8. Patients who switched previous licensed TKI treatment (imatinib, nilotinib or dasatinib) because of resistance
9. Patients treated with lower than standard TKI doses (imatinib 400mg daily, nilotinib 400mg twice daily or dasatinib 100mg daily) for tolerance reasons may be included, but will de-escalate to the same doses as for standard dose patients and will be analysed separately, as they could be seen as undertreated
10. Previous treatment with ponatinib or bosutinib. Patients who received interferon prior to commencing TKI (even if resistant to their interferon) are eligible, provided their response to TKI fits the entry criteria.
11. Pregnant or lactating women

12. Women of childbearing potential, including women whose last menstrual period was less than one year prior to screening, unable or unwilling to use adequate contraception from study start to one year after the last dose of protocol therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence

Date of first enrolment
01/08/2013

Date of final enrolment
01/07/2014

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Liverpool Cancer Research Centre
Liverpool
United Kingdom
L3 9TA

Sponsor information

Organisation
University of Liverpool (UK)

Sponsor details
Research and Business Services
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3 Brownlow Street
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United Kingdom
L69 3GL

Sponsor type
University/education

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

Organisation
The Royal Liverpool and Broadgreen University Hospitals NHS Trust

Sponsor details
Prescot Street
Liverpool
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United Kingdom
L7 8XP
-
abc@email.com

Sponsor type
Hospital/treatment centre

Website
www.rlbuht.nhs.uk

Organisation
University of Liverpool

Sponsor details

Sponsor type
Not defined

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

ROR
https://ror.org/04xs57h96

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
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2017		Yes	No
HRA research summary			28/06/2023	No	No