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Thrombin inhibition preoperatively in early breast cancer

Submission date	Recruitment status	[X] Prospectively registered
05/11/2015	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
05/11/2015	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
16/04/2021	Cancer	[_] Record updated in last year

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-a-blood-thinning-drug-for-women-with-breast-cancer-tip

Study website
https://www.lctu.org.uk/

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Additional identifiers

EudraCT/CTIS number
2014-004909-33

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
19731

Study information

Scientific Title
Thrombin Inhibition Preoperatively in early breast cancer (TIP study)

Acronym
TIP

Study objectives
Current study hypothesis as of 20/09/2018:
The aim of this study is to determine whether preoperative oral Factor Xa inhibitor (Rivaroxaban) in oestrogen receptor negative early breast cancer patients results in inhibition of tumour proliferation markers as determined by a reduction in tumour Ki67 from baseline (pretreatment) to post treatment (at time of surgical excision/research core biopsy).

Previous study hypothesis:
The aim of this study is to determine whether preoperative oral Factor Xa inhibitor (Rivaroxaban) in oestrogen receptor negative early breast cancer patients results in inhibition of tumour proliferation markers as determined by a reduction in tumour Ki67 from baseline (pretreatment) to post treatment (at time of surgical excision).

Ethics approval required
Old ethics approval format

Ethics approval(s)
First Medical Research Ethics Committee, 13/07/2015, ref: 15/NW/0406

Study design

Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Breast cancer

Interventions
Current interventions as of 20/09/2018:
Patients will be randomised into 2 groups in a 1:1 ratio as follows:

Group 1: Preoperative Rivaroxaban 20mg od and excisional approx 14 days later
Group 2: No Preoperative therapy with surgery/research core biopsy approx 14 days later

Patients should have their surgery/neoadjuvant chemotherapy booked prior to randomisation and scheduled for around two weeks ahead. All surgery will be completed to standard care.

Patients will return 2 weeks following the date of surgery for post-op complications and adverse events review. All further follow-up will be as per standard NHS practice with annual clinical and mammographic examination.

Previous interventions:
Patients will be randomised into 3 groups in a 1:1:1 ratio as follows (with the Rivaroxaban treatment groups being combined for primary endpoint analysis creating a 2:1 randomisation for Rivaroxaban vs. no treatment):

Group 1: Preoperative Rivaroxaban 20mg od and excisional approx 14 days later
Group 2: Preoperative Rivaroxaban 10mg od and excisional approx 14 days later
Group 3: No Preoperative therapy with surgery approx 14 days later

Patients should have their surgery booked prior to randomisation and scheduled for around two weeks ahead, as long it is within 31 days from diagnosis. All surgery will be completed to standard care.

Patients will return 2 weeks following the date of surgery for post-op complications and adverse events review. All further follow-up will be as per standard NHS practice with annual clinical and mammographic examination.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Rivaroxaban

Primary outcome measure
Current primary outcome measure as of 20/09/2018:
Percentage reduction in tumour Ki67 expression is measured using tumour core biopsies at baseline (pre-rivaroxaban), surgery/research core biopsy (post-rivaroxaban).

Previous primary outcome measure:
Percentage reduction in tumour Ki67 expression is measured using tumour core biopsies at baseline (pre-rivaroxaban), surgery (post-rivaroxaban).

Secondary outcome measures
Current secondary outcome measure as of 20/09/2018:
In post Rivaroxaban compared to pre- Rivaroxaban patient samples:
1. Reduction in tumour tissue expression of TF, TAT and PAR 1 is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
2. Reduction in tumour tissue expression of CD31 is measured using patient samples at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
3. Increase in tumour tissue expression of p27, cleaved Caspase 3 and TUNEL is measured using patient samples at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
4. Reduction in CTCs is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
5. Increase in circulating free DNA (cfDNA) and decrease in cfDNA Integrity (cfDI) is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
6. Reduction in plasma d-dimer, TF and TAT is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
7. Alterations in proteomics, correlating to tumour response is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)

In post Rivaroxaban compared to post placebo patient samples:
1. Reduction in MFE is measured using patient samples at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
2. Reduction in tumour tissue expression of TF, TAT and PAR 1 is measured using patient samples at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
3. Reduction in tumour tissue expression of CD31 is measured using patient samples at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
4. Increase in tumour tissue expression of p27, cleaved Caspase 3 and TUNEL is measured using patient samples at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
5. Reduction in CTCs is measured using patient samples at baseline (pre-rivaroxaban) and the

time of surgery/research core biopsy (post-rivaroxaban)
6. Increase in circulating free DNA (cfDNA) and decrease in cfDNA Integrity (cfDI) is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
7. Reduction in plasma d-dimer, TF and TAT is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)
8. Alterations in proteomics, correlating to tumour response is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery/research core biopsy (post-rivaroxaban)

Previous secondary outcome measure:
In post Rivaroxaban compared to pre- Rivaroxaban patient samples:
1. Reduction in tumour tissue expression of TF, TAT and PAR 1 is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
2. Reduction in tumour tissue expression of CD31 is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
3. Increase in tumour tissue expression of p27, cleaved Caspase 3 and TUNEL is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
4. Reduction in CTCs is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
5. Increase in circulating free DNA (cfDNA) and decrease in cfDNA Integrity (cfDI) is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
6. Reduction in plasma d-dimer, TF and TAT is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
7. Alterations in proteomics, correlating to tumour response is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)

In post Rivaroxaban compared to post placebo patient samples:
1. Reduction in MFE is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
2. Reduction in tumour tissue expression of TF, TAT and PAR 1 is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
3. Reduction in tumour tissue expression of CD31 is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
4. Increase in tumour tissue expression of p27, cleaved Caspase 3 and TUNEL is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
5. Reduction in CTCs is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
6. Increase in circulating free DNA (cfDNA) and decrease in cfDNA Integrity (cfDI) is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
7. Reduction in plasma d-dimer, TF and TAT is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
8. Alterations in proteomics, correlating to tumour response is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)

In post 20mg od Rivaroxaban compared to post 10mg Rivaroxaban patient samples (subgroup analysis):
1. Reduction in MFE is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
2. Reduction in tumour tissue expression of TF, TAT and PAR 1 is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
3. Reduction in tumour tissue expression of CD31 is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)

4. Increase in tumour tissue expression of p27, cleaved Caspase 3 and TUNEL is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
5. Reduction in CTCs is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
6. Increase in circulating free DNA (cfDNA) and decrease in cfDNA Integrity (cfDI) is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
7. Reduction in plasma d-dimer, TF and TAT is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)
8. Alterations in proteomics, correlating to tumour response is measured using patient samples at at baseline (pre-rivaroxaban) and the time of surgery (post-rivaroxaban)

Overall study start date
26/06/2015

Completion date
30/09/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 20/09/2018:
1. Provision of written informed consent.
2. World Health Organisation (WHO) performance status 0-1 with no deterioration over the previous 2 weeks
3. Patients must be able to swallow and retain oral medication
4. Female patients, age over 18, with histological confirmation of ER negative (ER Quick Score / Allred ≤5) invasive breast carcinoma
5. Any Her2 status
6. AJCC Stage 1- 3 with primary tumour in the breast amenable to biopsies
7. Scheduled to have definitive breast surgery 11 or more days after commencement of treatment or are able to take 11 or more days of rivaroxaban and have an additional core biopsy prior to starting neoadjuvant therapy.
8. Tumour size ≥10mm (large enough to provide sufficient tissue to be taken by core-cut or tru-cut biopsy (free-hand or under ultrasound guidance as per local protocols)).
9. As judged by the Investigator, no evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.
10. No clinically significant abnormalities in the full blood count, renal or liver biochemistry, as decided by the PI, and where the PI is unsure they should contact the CI or Clinical Coordinator for a final decision.
11. Estimated Glomerular Filtration Rate (eGFR) above 50 ml/min.

Previous inclusion criteria:
1. Female patients with histological confirmation of ER negative invasive breast carcinoma
2. Provision of written informed consent.
3. World Health Organisation (WHO) performance status 0-1 with no deterioration over the previous 2 weeks
4. Patients must be able to swallow and retain oral medication
5. AJCC Stage 1-3 with primary tumour in the breast amenable to biopsies
6. Scheduled to have definitive breast surgery 11 or more days after study entry

7. Tumour size =10mm (large enough to provide sufficient tissue to be taken by core-cut or tru-cut biopsy (freehand or under ultrasound guidance as per local protocols).
8. As judged by the site's Principal Investigator, no evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV)
9. Full blood count, renal and liver biochemistry (within 10% of laboratory normal limits)
10. EGFR above 50
11. Aged 18 or over

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 88; UK Sample Size: 88; Description: The study is powered on a change in Ki67 from baseline to post treatment. A sample size of 44 patients in the Rivaroxaban arm can achieve 80% power to detect a 0.6 standard deviation (SD) geometric mean Ki67-difference with a two-sided test at the alpha-level of 0.05.

Key exclusion criteria
Current exclusion criteria as of 20/09/2018:
1. Tumour size <10mm
2. Prior treatment for breast or other cancer (excluding non-melanoma skin cancer)
3. Concurrent anticoagulant therapy (excluding antiplatelet therapy such as aspirin or clopidogrel)
4. Concurrent treatment with azole-antimycotics (such as, ketoconazole, itraconazole, voriconazole and posaconazole); clarithromycin; HIV protease inhibitors; dronedarone; strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort); strong CYP3A4 or P-gp inhibitors
5. Major surgery within 4 weeks before the first dose of study treatment.
6. Conditions associated with an increased risk of bleeding:
6.1. Major surgery or trauma within the previous month
6.2. Haemorrhagic disorder or bleeding diathesis
6.3. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intraarticular bleeding
6.4. Gastrointestinal haemorrhage within the past year
6.5. Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
6.6. Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm
6.7. Need for anticoagulant treatment of disorders other than atrial fibrillation
6.8. Fibrinolytic agents within 48 hours of study entry
6.9. Uncontrolled hypertension (systolic blood pressure greater than 180 mm Hg and/or diastolic

blood pressure greater than 100 mm Hg
7. Known hypersensitivity or allergy to rivaroxaban and/or excipients
8. Participation in another interventional trial
9. Pregnant or lactating women
10. All women of reproductive potential, unless using at least one contraceptive precaution, which must be a condom for at least two weeks after the end of their treatment

Previous exclusion criteria:
1. Tumour size <10mm
2. Prior treatment for breast or other cancer (excluding non-melanoma skin cancer)
3. Concurrent anticoagulant therapy (excluding antiplatelet therapy such as aspirin or clopidogrel)
4. Concurrent treatment with azole-antimycotics (such as, ketoconazole, itraconazole, voriconazole and posaconazole); clarithromycin; HIV protease inhibitors; dronedarone; strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort); strong CYP3A4 or P-gp inhibitors
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6. Conditions associated with an increased risk of bleeding:
6.1. Major surgery or trauma within the previous month
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6.3. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intraarticular bleeding
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6.5. Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
6.6. Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm
6.7. Need for anticoagulant treatment of disorders other than atrial fibrillation
6.8. Fibrinolytic agents within 48 hours of study entry
6.9. Uncontrolled hypertension (systolic blood pressure greater than 180 mm Hg and/or diastolic blood pressure greater than 100 mm Hg
7. Known hypersensitivity or allergy to rivaroxaban and/or excipients
8. Participation in another interventional trial
9. Pregnant or lactating women
10. All women of reproductive potential, unless using at least two contraceptive precautions, one of which must be a condom for at least two weeks after the end of their treatment

Date of first enrolment
01/01/2016

Date of final enrolment
30/06/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospital of South Manchester
Wythenshawe Hospital
Southmoor Road
Wythenshawe
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United Kingdom
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Study participating centre
Macclesfield District General Hospital
Victoria Road
Macclesfield
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SK10 3BL

Study participating centre
North Manchester General Hospital
Delaunays Road
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United Kingdom
M8 5RB

Study participating centre
The Royal Liverpool University Hospital
Prescot Street
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United Kingdom
L7 8XP

Study participating centre
The Royal Bolton Hospital
Minerva Road
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
Leeds Teaching Hospitals
Beckett Street

Leeds
United Kingdom
LS9 7TF

Study participating centre
Clatterbridge Hospital
Wirral University Teaching Hospitals NHS Foundation Trust
Clatterbridge Road
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United Kingdom
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Study participating centre
Churchill Hospital
Oxford Health NHS Foundation Trust
Old Road
Headington
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OX3 7LJ

Sponsor information

Organisation
Manchester University NHS Foundation Trust

Sponsor details
Southmoor Road
Wythenshawe
Manchester
England
United Kingdom
M23 9LT

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The results from different centres will be analysed together and published in a peer reviewed journal.

Intention to publish date
30/09/2022

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	27/08/2020	02/09/2020	Yes	No
HRA research summary			28/06/2023	No	No