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FEASIBILITY of IBIS 3. An International Breast Intervention Study investigating prevention of late recurrence in ER+ breast cancer survivors following 5 years of adjuvant treatment

Submission date
21/11/2014

Recruitment status
No longer recruiting

Registration date
11/12/2014

Overall study status
Stopped

Last Edited
18/06/2020

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-extended-treatment-following-5-years-hormone-therapy-breast-cancer-ibis-3-feasibility

Contact information

Type(s)
Public

Contact name
Prof Jack Cuzick

Contact details
Centre for Cancer Prevention
Wolfson Institute of Preventive Medicine
Charterhouse Square
London
United Kingdom
EC1M 6BQ
+44 (0)20 7882 3518
j.cuzick@qmul.ac.uk

Type(s)
Scientific

Contact name
Dr Mangesh Thorat

ORCID ID
https://orcid.org/0000-0001-8673-5320

Contact details
Centre for Cancer Prevention
Wolfson Institute of Preventive Medicine
Barts & The London School of Medicine and Dentistry
Queen Mary University of London
London
United Kingdom
EC1M 6BQ
+44 (0)20 7882 3890 (fax)
m.thorat@qmul.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2014-004430-26

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
FEASIBILITY of IBIS 3. An International Breast Intervention Study investigating prevention of late recurrence in ER+ breast cancer survivors following 5 years of adjuvant treatment

Acronym
IBIS 3 (Feasibility)

Study objectives
IBIS 3 is designed to continue the work of IBIS-I and IBIS-II in determining whether a chemo-preventive strategy towards breast cancer is effective. Late recurrence of oestrogen receptor positive (ER+) breast cancer is a well-known problem, with high recurrence rates being seen for at least 20 years after diagnosis. In fact, over half of all recurrences in ER+ breast cancer occur more than 5 years after the primary tumour diagnosis. These include true recurrences and new primary tumours. Although reduced from about 2.5%/year with tamoxifen to 2%/year with 5 years of an aromatase inhibitor in the ATAC trial, the 10 year recurrence rate does not fall below 2%/year (Cuzick et al, 2010). The ATAC trial indicates that ER, PgR and HER2 do not provide substantial prognostic information in the post 5-year treatment period. It shows that Ki-67 has a minimal effect whereas baseline nodal status and tumour size (≥ 2cm) continue to have prognostic value (Sestak et al, 2013).

Late re-treatment of breast cancer is an important approach for dealing with the problem of late recurrence. Diminished endocrine control is well documented and other new or synergistic approaches are likely to be more effective. This approach will also inform on the preventive

action of these agents both alone and in combination not only on elimination of metastases but also on new primary tumours. Because a substantial number of late recurrences are in fact new tumours, this approach will also inform on the preventive action of these agents both alone and in combination.

The main IBIS 3 trial will directly address the issue of late recurrence in breast cancer survivors. The main goal will be to reduce late recurrence with the combination of three different drug therapies. Specifically, it will evaluate the impact of metformin and/or an aromatase inhibitor (anastrozole or letrozole or exemestane) and/or zoledronic acid in a 2x2x2 factorial trial. Of particular interest will be any positive detection of any synergism between these agents.

The main trial will explore mechanisms of drug action and identify which patients are at greatest risk of late recurrence, including both local, regional and distant metastases of the primary tumour as well as new tumours (mostly contralateral), using a range of tests which may include circulating tumour DNA, IHC4, PAM50, and tumour methylation profiles.

This feasibility study will look at the viability of recruiting to the main trial; assess recruitment rates, inform on number of sites required for the main trial, treatment adherence and the use of recruiting through GP surgeries local to sites via the PCRN/LCRN. The study will also determine the feasibility of the use of email for data collection of PROs from patients and assess the acceptability of investigations, such as providing blood samples and questionnaires required for the main trial.

The decision rule for moving to the main trial will be recruitment of at least 80 patients within a year and that at least 20% of eligible patients approached agree to join the trial.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Hampstead Ethics Committee, 08/06/2015, ref: 15/LO/0833

Study design
Interventional multi-centre CTIMP RCT 2x2x2 factorial design

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Hormone receptor positive breast cancer recurrence

Interventions
Metformin and zoledronic acid will be evaluated when combined with an aromatase inhibitor (anastrozole, letrozole or examestane) in a 2x2x2 factorial design.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Aromatase inhibitor (anastrozole, letrozole or examestane), metformin, zoledronic acid

Primary outcome(s)
Primary objective is to determine acceptability and feasibility of recruitment, recruitment rate and number of sites required for main trial.
Primary endpoint is the recruitment of 100 patients within 12 months. Assessment method is recruitment numbers via randomisation figures and screening logs.

Key secondary outcome(s))
Secondary objectives are:
1. To determine reasons for non-participation/drop-outs and address these for main trial (endpoint: recruitment and follow-up of 100 patients; assessment method: analysis of screening logs to understand reasons for non-participation)
2. To evaluate treatment adherence and reasons for stopping (endpoint: 6 monthly follow-up; assessment method: data collected on CRFs, PROs [FACT-ES, EQ5DL], Kaplan Meier curves)
3. To determine reasons for non-adherence and address for main trial (endpoint: 6 monthly follow-up; assessment method: data collected on CRFs, PROs [FACT-ES, EQ5DL])
4. To assess the use of referral through GP surgeries as PICs local to sites via the PCRN/LCRN (endpoint: the recruitment of 100 patients; assessment method: recruitment method captured by CRF and assessment of referral letters)
5. To investigate feasibility of the use of email for data collection of PROs from patients (enpoint: at baseline + asked again at 12 and 24 months to see if email use increases with time; assessment method: comparison of numbers of patients providing data by email or by post and quality and completeness of that data)
6. To assess acceptability of investigations for main trial (endpoint: at 12 months and ongoing until trial ends; assessment method: number of patients providing blood samples [data on CRF], PRO data [FACT-ES, EQ5DL])

Completion date
26/03/2018

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Current inclusion criteria as of 30/03/2017:
1. Informed Consent
2. ≤ 75 years
3. Post-menopausal women confirmed by previous AI use only
4. Previous ER+ breast cancer treated by endocrine therapy. ER+ is equivalent to an Allred/Quick score of 3 or above. Additional treatment with trastuzumab (if Her2+) and chemotherapy are allowed.
5. Surgery for breast cancer plus 5 years adjuvant endocrine therapy (at least 4 years with AI completed within the last 6 years; therefore 5-11 years from diagnosis)

6. Breast cancer must have been node positive AND/OR ≥2cm in size (measurement based on invasive tumour)
7. A bilateral mammogram (unless unilateral mastectomy in which case unilateral mammogram) must have been taken within the last year and not show any evidence of breast cancer. Women who have had a bilateral mastectomy, where contralateral mastectomy was either prophylactic or was performed to treat breast cancers diagnosed at the same time, are eligible and a mammogram is not required in this case.
8. A baseline bone mineral density (BMD) scan within the last year; DXA must include hip (femoral neck or proximal femur) AND lumbar spine and can include forearm.
9. Low BMD (where T-score is -4.0 ≤T≤ -2.0) women are eligible for metformin and aromatase inhibitor treatments. This must be managed in accordance with local clinical procedures for treatment of osteoporosis i.e., take bisphosphonate treatment and have regular DXA scans

Previous inclusion criteria:
1. Informed consent
2. ≤ 75 years old
3. Post-menopausal women (defined as at least 12 months since last period)
4. Previous ER+ (or PR+) breast cancer treated by endocrine therapy. ER+ is equivalent to an Allred/Quick score of 3 or above. Additional trastuzumab (if Her2+) and chemotherapy are allowed.
5. Surgery for breast cancer plus 4-6 years adjuvant endocrine therapy (at least 4 years with AI completed within the last 3 years; therefore maximum of 9 years from diagnosis)
6. Breast cancer must have been node positive (macrometastases) AND/OR ≥2cm
7. A bilateral mammogram (unless unilateral mastectomy in which case unilateral mammogram) must have been taken within the last year and not show any evidence of breast cancer. Women who have had a bilateral mastectomy are eligible and a mammogram is not required in this case.
8. A baseline bone mineral density scan within the last year; DXA must include hip (femoral neck or proximal femur) AND lumbar spine and can include forearm.
9. Low BMD (where T-score is -4.0 ≤T≤ -2.0) and no more than one known low trauma vertebral fracture AND/OR high FRAX score (http://www.shef.ac.uk/FRAX/tool.aspx) are eligible for metformin and aromatase inhibitor treatments. This must be managed in accordance with local clinical procedures for treatment of osteoporosis i.e., take bisphosphonate treatment and have regular DXA scans.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
89

Key exclusion criteria

Current exclusion criteria as of 30/03/2017:
1. Any recurrence or clinical suspicion of active breast cancer (including DCIS)
2. Any other previous cancer (apart from original breast cancer) (except non-melanoma skin cancer or in situ cancer of the cervix).
3. Current (or intended) use of oestrogen-based hormone replacement therapy (HRT)
4. Type I diabetes
5. Type II diabetes AND osteoporosis
6. T-scores of less than minus four, or two or more known low trauma vertebral fractures
7. Abnormal renal function as classified as eGFR < 45mls/min. – If possible the CKD-EP1 equation should be used to calculate eGFR but the Cockroft-Gault formula is acceptable. See Appendix 3 for formulae and dose reduction schedule.
8. Any severe concomitant disease, e.g congestive cardiac failure, that would, at the discretion of the investigator, put patient at unusual risk or confounds the results of the study. Reference should be made to the appropriate Summary of Product Characteristics (SmPC) of each study drug
9. Current continual treatment with glucocorticoids for 4 weeks or more
10. Any medical condition that would significantly interfere with the ability to accept the study drugs.
11. Psychologically and physically unsuitable for two years of drug therapy.
12. Treatment with an unlicensed or experimental drug during 30 days before randomisation.

Excluded from metformin randomisation only
13. Type II diabetics (or those with baseline fasting glucose > 7.0 mmol/L) but must be on antidiabetic medication
14. Known hypersensitivity or intolerance to metformin
15. Currently taking meglitinides, sulfonylureas, thiazolidinediones (glitazones) or insulin
16. History of acidosis of any type
17. Habitual intake of 3 or more units of alcohol per day

Excluded from zoledronic randomisation only
18. Low BMD (where T-score is -4.0 ≤T≤ -2.0). This must be managed in accordance with local clinical procedures for treatment of osteoporosis i.e., take bisphosphonate treatment and have regular DXA scans. See Appendix 4 for definitions.

Excluded from AI randomisation only
19. Currently being treated by extended AI
20. Current use (or intention to use) raloxifene, tamoxifen or any other SERM

Previous exclusion criteria:
1. Any recurrence or clinical suspicion of active breast cancer (including DCIS)
2. Any other previous cancer (apart from original breast cancer) in the past 5 years (except non-melanoma skin cancer or in situ cancer of the cervix)
3. Current treatment (or intended use) of oestrogen-based hormone replacement therapy (HRT)
4. Type I diabetes
5. Diabetes (Types I and II) AND osteoporosis
6. T-scores of less than minus four, or two or more known low trauma vertebral fractures
7. Abnormal renal function as classified as eGFR < 40ml/min. If possible the CKD-EP1 equation should be used to calculate eGFR but the Cockroft-Gault formula is acceptable
8. Any severe concomitant disease, e.g. congestive cardiac failure, that would, at the discretion of the investigator, put patient at unusual risk or confounds the results of the study. Reference should be made to the appropriate Summary of Product Characteristics (SmPC) of each study drug

9. Current continual treatment with glucocorticoids for 4 weeks or more
10. Any medical condition that would significantly interfere with the ability to accept the study drugs
11. Psychologically and physically unsuitable for two years of drug therapy
12. Treatment with an unlicensed or experimental drug during 30 days before randomisation

Excluded from metformin randomisation only:
1. Type II diabetics (or those with baseline fasting glucose > 7.0 mmol/L) but must be on antidiabetic medication
2. Known hypersensitivity or intolerance to metformin
3. Currently taking meglitinides, sulfonylureas, thiazolidinediones (glitazones) or insulin
4. History of acidosis of any type
5. Habitual intake of three or more units of alcohol per day

Excluded from zoledronic randomisation only:
1. Low BMD (where T-score is -4.0 ≤T≤ -2.0) and no more than one known low trauma vertebral fracture AND/OR high FRAX score (http://www.shef.ac.uk/FRAX/tool.aspx)

Excluded from AI randomisation only:
1. Currently being treated by extended AI
2. Current use (or intention to use) raloxifene, tamoxifen or any other SERM

Date of first enrolment
26/09/2016

Date of final enrolment
26/09/2017

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Borders General Hospital
Melrose
United Kingdom
TD6 9BS

Study participating centre

Weston Park Hospital
Sheffield
United Kingdom
S10 2SJ

Study participating centre
Christie NHS Foundation Trust
Manchester
United Kingdom
M20 4BX

Study participating centre
Cardiff University Hospital NHS Trust
Cardiff
United Kingdom
CF14 4XW

Study participating centre
St Bartholomew's Hospital
London
United Kingdom
EC1A 7BE

Study participating centre
Ninewells Hospital
Dundee
United Kingdom
DD1 9SY

Study participating centre
Imperial College Healthcare NHS Trust
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre

Doncaster Royal Infirmary
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Study participating centre
Macclesfield District General Hospital
Victoria Road
Macclesfield
United Kingdom
SK10 3BL

Study participating centre
North Tyneside General Hospital
Rake Lane
North Shields
United Kingdom
NE29 8NH

Study participating centre
Pinderfields Hospital
Aberford Road
Wakefield
United Kingdom
WF1 4DG

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

Study participating centre
Poole Hospital NHS Foundation Trust
Longfleet Road
Poole
United Kingdom
BH15 2JB

Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

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

Funder Name
Australia and New Zealand Breast Cancer Trials Group (ANZBCTG)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from ibis3@qmul.ac.uk

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results	barriers to recruitment presented at 4th International Clinical Trials Methodology Conference (ICTMC) and the 38th Annual Meeting of the Society for Clinical Trials	01/05/2017	16/06/2020	No	No
Basic results			11/06/2020	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Plain English results				No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes