ISRCTN13877559 https://doi.org/10.1186/ISRCTN13877559

Gut bacteria and their association with chemotherapy response in early breast cancer patients

Submission date 27/05/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 06/07/2021	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 24/04/2023	**Condition category** Cancer	[_] 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-looking-at-how-the-microbiome-affects-breast-cancer-treatment-neo-microbe-breast-study

Background and study aims
The way breast cancer responds to chemotherapy is not always the same between patients. Within our gut, there are lots of bacteria that play important roles in keeping us healthy. We believe that these bacteria may also determine which patients achieve the best response to chemotherapy. We know that diet and other interventions can change the bacteria. In this research, we hope to identify certain patterns in the bacteria that link with what type of response a patient has to chemotherapy. Overall, we hope to identify specific trends in gut bacteria, which are associated with a better response to chemotherapy. With future research we would then hope to determine how to recreate these favourable gut bacterial trends in patients, to help them achieve the best response to chemotherapy.

To do this we will look at blood, stool and tumour samples from women who are having a course of chemotherapy before surgery for breast cancer. We will look into the role that the immune system, gut products and tissues surrounding cancer may have in working alongside the bacteria. We will try to understand how the bacteria are linked with chemotherapy side effects. We will also collect stool samples from healthy volunteers, who do not have cancer, to compare to samples from the patients with breast cancer.

Who can participate?
Patients diagnosed with early breast cancer, which is “HER2-positive” or “triple-negative” that are planned to have neoadjuvant chemotherapy (chemotherapy before surgery) at the Beatson West of Scotland Cancer Centre or the New Victoria Hospital, Glasgow. All patients will live within approximately 20 miles of Glasgow Royal Infirmary.
Female healthy volunteers will also be recruited.

What does the study involve?
The following samples and data will be collected from patients receiving standard of care chemotherapy:

Stool samples are collected at 2 time points: prior to commencing chemotherapy and after completion of chemotherapy.
Research blood samples will be collected at 1 time point, prior to commencing chemotherapy.
Archival Tumour samples will be collected from the patients' diagnostic core biopsies (standard of care (SOC) NHS sample).
Clinical Data: recording of specific treatment related toxicities (febrile neutropenia and diarrhoea) and specific concomitant medications; will be made at each clinic visit for pre-assessment for chemotherapy (SOC).
Dietary assessment: The patient will complete an EPIC-Norfolk FFQ at 2 time points: prior to commencing chemotherapy and after completion of chemotherapy. This can be completed in the clinic or at home; with the support of a researcher (over the phone or a video-call).
Response Assessment Following surgery, pathology reports will be reviewed and patients will be categorised into whether they achieved a pCR or non-pCR (SOC).

Healthy Volunteers
Stool sample collected once.

What are the possible benefits and Risks of Participating?
There are no direct therapeutic benefits from this study. Participation may help patients diagnosed with breast cancer in the future as we hope to identify particular patterns in the gut bacteria, which could offer potential for future interventional studies.

Where is the study run from?
University of Glasgow (UK)

When is the study starting and how long is it expected to run for?
February 2021 to September 2025

Who is funding the study?
Chief Scientist Office, the University of Glasgow and the Beatson Cancer Charity (UK)

Who is the main contact?
Dr Kirsty Ross, kirsty.ross.2@glasgow.ac.uk

Contact information

Type(s)
Public

Contact name
Dr Kirsty Ross

ORCID ID
https://orcid.org/0000-0002-7553-4109

Contact details

University of Glasgow
Wolfson Wohl Cancer Research Centre
Garscube Estate
Switchback Road
Glasgow
United Kingdom
G61 1QH
+44 (0)7894631669
kirsty.ross.2@glasgow.ac.uk

Type(s)
Scientific

Contact name
Dr Kirsty Ross

Contact details
University of Glasgow
Wolfson Wohl Cancer Research Centre
Garscube Estate
Switchback Road
Glasgow
United Kingdom
G61 1QH
07894631669
kirsty.ross.2@glasgow.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
293817

Protocol serial number
NEOMICROBE_2021

Study information

Scientific Title
The NEO-MICROBE BREAST Study: Neoadjuvant chemotherapy and the gut microbiome in breast cancer

Study objectives
The gut microbiome impacts chemotherapy response in early breast cancer patients receiving neoadjuvant chemotherapy.

Pathological complete response (pCR) following a course of neoadjuvant chemotherapy strongly predicts improved long-term survival in patients with early breast cancer. This study will test the hypothesis that the composition and functional status of the gut microbiome prior to

commencing chemotherapy is associated with pCR. In addition, the study will explore putative mechanisms including 1) modulation of the immune microenvironment and 2) alterations in circulating metabolites and cytokines.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/07/2021, West of Scotland Research Ethics Committee 4 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 3140213; WoSREC4@ggc.scot.nhs.uk), ref: 21/WS/0078

Primary study design
Observational

Study design
Prospective observational non-interventional study

Study type(s)
Other

Health condition(s) or problem(s) studied
Breast cancer (Triple Negative and HER2+ subtypes)

Interventions
Sample Collection & Study-Related Procedures
• Stool samples are collected at 2 time points: prior to commencing chemotherapy and after completion of chemotherapy
• Research blood samples will be collected at 1 time point, prior to commencing chemotherapy
• Archival Tumour samples will be collected from the patients' diagnostic core biopsies (standard of care (SOC) NHS sample)
• Clinical Data: recording of specific treatment related toxicities (febrile neutropenia and diarrhoea) and specific concomitant medications; will be made at each clinic visit for preassessment for chemotherapy (SOC)
• Dietary assessment: The patient will complete an EPIC-Norfolk FFQ at 2 time points: prior to commencing chemotherapy and after completion of chemotherapy.

Intervention Type
Other

Primary outcome(s)
Measured using stool samples collected at 2 time points, at baseline before commencing chemotherapy (T1) and after completion of chemotherapy but before surgery (T2) in patients. Healthy Volunteers will provide a stool sample at a single timepoint.
1. Baseline taxonomic richness for patients achieving pCR (ypT0/is ypN0) vs. non-pCR. Taxonomic richness will be calculated according to rarefied richness (other alpha diversity index measures will be explored.)
2. Stool SCFA concentration levels (acetate, butyrate and propionate) for patients achieving pCR (ypT0/is ypN0) vs. non-pCR
3. Taxon relative abundance for patients achieving pCR (ypT0/is ypN0) vs. non-pCR

Key secondary outcome(s)
Exploratory Endpoints will be investigated using the following samples/data from patients:
• Stool samples collected at 2 time points, at baseline before commencing chemotherapy (T1) and after completion of chemotherapy but before surgery (T2).
• Blood samples collected at 1 time point (T1).
• Dietary information collected at 2 time points (T1 and T2).
• Clinical data collected at multiple time points (dependent on participants' total number of cycles of chemotherapy received).
Healthy Volunteers will provide a stool sample at a single timepoint.

Exploratory Endpoints:
This study will investigate the association between gut microbial composition and function and /or SCFA levels with:
1.1. Immune infiltration of tumour, utilising immunohistochemistry (IHC) and gene expression analysis
1.2. Systemic immune status with assessment of cytokines and other immune surrogate markers from peripheral blood (CRP and albumin) and stool (calprotectin)
2. The tumour-microenvironment, including IHC staining of collagen
3. Metabolomic analysis of plasma samples by Liquid Chromatography-Mass Spectrometry (LC-MS) and other techniques
4. Episodes of febrile neutropenia and/or diarrhoea (CTCAE v4.0 grading)
5. Assessment of nutritional intake utilising EPIC-Norfolk food frequency questionnaire (FFQ) at baseline. Nutritional intake will be analysed using Windiets or Nutritics software
6. Pre- and post- chemotherapy stool samples compared for patients achieving pCR (ypT0/is ypN0) vs. non-pCR
7. Other relevant pathways and markers putatively linked to pCR and the gut microbiome may also be investigated. The inferred microbial composition of healthy control samples will be used to assess dysbiosis

Completion date
01/09/2025

Eligibility

Key inclusion criteria
1. Unequivocal evidence of metastatic disease.
2. History of active, uncontrolled gastrointestinal (GI) disorders, including:
2.1. Inflammatory bowel disease (IBD) including ulcerative colitis (mild-moderate-severe) and Crohn's disease (mild-moderate-severe) or indeterminate colitis
2.2. Irritable bowel syndrome (IBS) (severe or on regular medication)
2.3. Persistent infectious gastroenteritis, colitis or gastritis, persistent or chronic diarrhoea of unknown aetiology or clostridium difficile infection (recurrent)
3. Major gastrointestinal surgery with the exception of appendicectomy and cholecystectomy. Any bowel resection at any time.
4. Treatment with systemic corticosteroids (intravenous or oral) or other immunosuppressive therapy for any other condition (including but not limited to prednisolone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumour necrosis factor [TNF] agents) within 28 days prior to Cycle 1 of neoadjuvant chemotherapy. The use of inhaled corticosteroids is allowed, as well as the use of mineralocorticoids (e.g. fludrocortisones) and low-dose supplemental corticosteroids for adrenocortical insufficiency and for orthostatic hypotension.

5. Confirmed or suspected state of immunodeficiency (primary or acquired) including HIV, hepatitis B and hepatitis C infection
6. Recent COVID-19 infection (≤ 28 days) or close contact with someone known to test positive (≤ 14 days).
7. Pregnant and/or breastfeeding individuals
8. Other severe or uncontrolled systemic disease or evidence of any other significant disorder or lab finding that makes it undesirable for the patient to participate in the study

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
100

Key exclusion criteria
1. History of active, uncontrolled gastrointestinal (GI) disorders, including:
1.1. Inflammatory bowel disease (IBD) including ulcerative colitis (mild-moderate-severe) and Crohn's disease (mild-moderate-severe) or indeterminate colitis
1.2. Irritable bowel syndrome (IBS) (severe or on regular medication)
1.3. Persistent infectious gastroenteritis, colitis or gastritis, persistent or chronic diarrhoea of unknown aetiology, clostridium difficile infection (recurrent) or helicobacter pylori infection (untreated)
2. Major GI surgery with the exception of appendicectomy and cholecystectomy. Any bowel resection at any time.
3. History of breast malignancy at any time or non-breast malignancy, requiring systemic therapy within the last 24 months.
4. Use of oral antibiotics within the last 6 weeks
5. Using a food exclusion diet due to diagnosis of food allergies or other food intolerances.
6. Individuals on medication requiring regular medical consultations (≤ 6 monthly)
7. Routine use of proprietary probiotics or prebiotics; in tablets, capsules or in powder form.
8. Recent COVID-19 infection (≤ 28 days) or close contact with someone known to test positive (≤ 14 days).
9. Pregnant and/or breastfeeding individuals
10. Other severe or uncontrolled systemic disease or evidence of any other significant disorder that makes it undesirable for the patient to participate

Date of first enrolment
01/11/2021

Date of final enrolment
31/10/2023

Locations

Countries of recruitment

United Kingdom

Scotland

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
The New Victoria Hospital
52 Grange Road
Glasgow
United Kingdom
G42 9LF

Sponsor information

Organisation
NHS Greater Glasgow and Clyde

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Government

Funder Name
Chief Scientist Office, Scottish Government Health and Social Care Directorate

Alternative Name(s)
Chief Scientist Office, Scottish Government Health Directorate CSO, Chief Scientist Office, Scottish Government Health Directorates, Chief Scientist Office of the Scottish Government Health Directorates, Scottish Government Health and Social Care Directorate of the Chief Scientist Office, Scottish Government Health Directorate Chief Scientist Office, The Chief Scientist Office, CSO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
University of Glasgow

Alternative Name(s)
The University of Glasgow

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Funder Name
Beatson Cancer Charity

Alternative Name(s)

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 current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No