# Tailoring treatment for HER2-positive early breast cancer

| <b>Submission date</b> 05/10/2021 | Recruitment status Recruiting  Overall study status Ongoing  Condition category Cancer | <ul><li>[X] Prospectively registered</li><li>[X] Protocol</li><li>Statistical analysis plan</li></ul> |  |  |
|-----------------------------------|--|---|--|--|
| Registration date                 |  |   |  |  |
| 11/10/2021                        |  | Results   |  |  |
| Last Edited                       |  | Individual participant data   |  |  |
| 10/07/2025                        |  | [X] Record updated in last year   |  |  |

#### Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-personalised-treatment-for-early-her2-positive-breast-cancer-her2-radical

#### Background and study aims

Patients with the "HER2-positive" type of early breast cancer (HER2+ EBC) usually receive a course of drug treatment as well as surgery. This drug treatment improves chances of cure by destroying any breast cancer cells that might have already begun to spread. The aim is to reduce the burden of treatment and the risk of serious long-term side effects for some patients with HER2+ EBC. The researchers want to find out if they can adjust the amount of drug treatment given to patients after surgery according to the way the cancer initially responds to drug treatment before surgery.

#### Who can participate?

Patients aged 16 years and over with HER2+ EBC treated with neoadjuvant chemotherapy, pertuzumab and trastuzumab, who have a pathological complete response (pCR) at surgery.

#### What does the study involve?

Before entry into the study, a review of medical history and a pregnancy test (for all women who are able to get pregnant) will be conducted to determine if a patient is eligible to enter. Following study entry patients will continue to receive trastuzumab until a total of 9 cycles (about 6 months) of treatment have been given. This number of cycles includes the trastuzumab treatment received before entering the study. For patients who do not take part in the study it is likely that 17 or 18 cycles (about 1 year in total) of trastuzumab would be given. For some patients, the possibility of receiving pertuzumab and/or chemotherapy after surgery may have been discussed by their doctor, however, patients who have entered HER2-RADICAL will not receive pertuzumab or any further chemotherapy after surgery. Patients will continue to receive trastuzumab in the same way that they would receive it if they were not taking part in the study. This may be as an injection under the skin or through a drip in the arm. During trastuzumab treatment the following assessments will be conducted. Before each cycle of trastuzumab the patient will have a discussion with their study doctor or nurse to document if there have been changes in their health since the last visit. Patients will continue to have their heart function measured with an echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan in the

same way that would have happened if they were not taking part in the study. In many hospitals this will be done around 4 and 8 months after starting trastuzumab. Patients may receive other preventative treatments like hormone treatment, radiotherapy and bisphosphonates, just as they would if they were not taking part in this study. The study research team will request a sample of tumour tissue collected at the time of initial diagnosis and a copy of the pathology report. They will also ask for tissue samples (or images of tissue samples) collected at the time of surgery from about 100 study participants. These samples and images will be analysed by the research team to ensure that they agree with the diagnosis of pCR made by the hospital pathologist. About 30 days after the last cycle of trastuzumab, patients will have a discussion with their study doctor to document if there have been any changes in their health since the last visit. After treatment has finished, patients will have a mammogram and a follow up once a year for at least 5 years. The study research team also plan to collect routine information about the health of study participants, such as hospital admissions, information relating to their cancer, any treatments they might go on to receive and continued information about their overall health and wellbeing, from NHS databases.

What are the possible benefits and risks of participating?

By receiving a shorter duration of antibody treatment (trastuzumab and pertuzumab) and by not receiving adjuvant chemotherapy (if this had been discussed), patients may benefit from having fewer visits for treatment as well as a lower risk of short- and long-term side effects. Patients who take part in this study will be less likely to have some of these side effects because treatment is given for a shorter time.

By receiving less treatment patients may have a slightly increased risk of their cancer coming back. It is well known that patients who are suitable for this study have a high chance of remaining cancer-free with current treatment: about 96 in every 100 patients (96%) will remain free of cancer 3 years after diagnosis and about 94 in every 100 (94%) will remain cancer-free at 5 years from diagnosis. Based on previous research the study team think it is likely that carefully reducing treatment, as planned in this study, may not increase the risk of the cancer returning or may only increase the risk by a very small amount that could be balanced by the benefits of fewer side effects. However, this is not known for certain and this is why this research is being done. An independent group of scientists and doctors will closely monitor the progress and early results of the study to ensure that the continuation of the study remains safe and in the best interest of those patients volunteering to take part.

Where is the study run from? The Institute of Cancer Research (ICR) (UK)

When is the study starting and how long is it expected to run for? December 2019 to March 2032

Who is funding the study? National Institute for Health Research – Health Technology Assessment (HTA) Programme (UK)

Who is the main contact? Katie Goddard her2radical-icrctsu@icr.ac.uk

## Contact information

**Type(s)** Scientific

#### Contact name

Dr Katie Goddard

#### Contact details

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## Additional identifiers

#### Clinical Trials Information System (CTIS)

2021-001240-10

#### Integrated Research Application System (IRAS)

292122

#### ClinicalTrials.gov (NCT)

Nil known

#### Protocol serial number

CPMS 50425, IRAS 292122

## Study information

#### Scientific Title

The HER2-RADICAL study (Response ADaptive CAre pLan) – tailoring treatment for HER2 positive early breast cancer

#### Acronym

**HER2-RADICAL** 

#### Study objectives

HER2-RADICAL seeks to test the hypothesis that a pathological complete response (pCR) to preoperative chemotherapy and anti-HER2 drug therapy can be used as a functional response biomarker to select patients who can safely receive less intensive personalised therapy, with minimal or no loss of efficacy in the population.

### Ethics approval required

Old ethics approval format

#### Ethics approval(s)

Approved 20/08/2021, London - South East Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8085; londonsoutheast. rec@hra.nhs.uk), REC ref: 21/LO/0529

#### Study design

Interventional non-randomized study

#### Primary study design

Interventional

#### Study type(s)

Treatment

#### Health condition(s) or problem(s) studied

HER2-positive early breast cancer

#### **Interventions**

Current interventions as of 21/12/2023:

Patients taking part in the study will continue treatment with trastuzumab until 9 cycles have been completed (rather than 18 cycles), including those cycles administered prior to study entry. No more pertuzumab will be given after study registration, and patients will not receive chemotherapy after surgery. Some patients may not receive a type of chemotherapy called an anthracycline if this was being deferred to after surgery. Any other treatment that might have been recommended (like hormone therapy or radiotherapy) will be given as normal.

Trastuzumab (original or biosimilar) should be given every 3 weeks to complete a total of 9 cycles including those cycles administered prior to study entry; the number of cycles given within the HER2-RADiCAL study is altered according to the number of cycles received prior to study entry. Trastuzumab may be administered via IV or subcutaneous routes in accordance with the standard practice at the site and will be administered as per the SmPC and local guidelines. Subcutaneous trastuzumab is administered at a dose of 600 mg every 3 weeks. Intravenous trastuzumab is administered at a dose of 6 mg/kg body weight every 3 weeks (with a loading dose of 8 mg/kg if required). No dose reductions are permitted.

#### Previous interventions:

Patients taking part in the study will continue treatment with trastuzumab until 9 cycles have been completed (rather than 18 cycles), including those cycles administered prior to study entry. No more pertuzumab will be given after study registration, and patients will not receive a type of chemotherapy called an anthracycline, or any other type of chemotherapy, after surgery. Any other treatment that might have been recommended (like hormone therapy or radiotherapy) will be given as normal.

Trastuzumab (original or biosimilar) should be given every 3 weeks to complete a total of 9 cycles including those cycles administered prior to study entry; the number of cycles given within the HER2-RADiCAL study is reduced according to the number of cycles received prior to study entry. Trastuzumab may be administered via IV or subcutaneous routes in accordance with the standard practice at the site and will be administered as per the SmPC and local guidelines. Subcutaneous trastuzumab is administered at a dose of 600 mg every 3 weeks. Intravenous trastuzumab is administered at a dose of 6 mg/kg body weight every 3 weeks (with a loading dose of 8 mg/kg if required). No dose reductions are permitted.

#### Intervention Type

Drug

#### Phase

Not Applicable

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

Trastuzumab

#### Primary outcome(s)

Relapse-free-interval (RFI), defined as time from registration to invasive local or distant relapse or death from breast cancer in the absence of a previously identified relapse (intercurrent deaths and second primary cancers censored). The primary timepoint of interest will be 3 years.

#### Key secondary outcome(s))

#### Efficacy:

- 1. Relapse-free-survival (RFS) defined as time from registration to invasive local or distant relapse or death from any cause (second primary cancers censored)
- 2. Invasive breast cancer-free survival (iBCFS) defined as time from registration to invasive local or distant relapse or ipsilateral or contralateral invasive second primary breast cancer (non-breast second primary cancers censored) or death from any cause
- 3. Invasive disease-free survival (iDFS) defined as time from registration to invasive local or distant recurrence, new invasive second cancer or death from any cause
- 4. Distant recurrence-free interval (DRFI) defined as time from registration to distant recurrence or death from any cause (second primary cancers and intercurrent deaths censored)
- 5. Breast cancer-free interval (BCFI) defined as time from registration to invasive local or distant relapse, or ipsilateral or contralateral invasive second primary breast cancer or DCIS or death from breast cancer in the absence of a previously identified relapse (intercurrent deaths and second primary cancers censored)
- 6. Overall survival defined as time from registration to death from any cause

#### Other:

- 1. Treatment pathway adherence: non-adherence is defined as the proportion of patients who receive >9 cycles of trastuzumab or who receive further adjuvant systemic anti-HER2 treatment (e.g. pertuzumab) or chemotherapy prior to recurrence or second primary
- 2. Cost-effectiveness: quality-adjusted life-years derived from a health economic model developed using clinical trial and real-world data at 3 and 5 years after study entry

## Completion date

28/03/2032

## **Eligibility**

#### Key inclusion criteria

Current inclusion criteria as of 21/12/2023:

- 1. Female or male, age ≥16 years
- 2. Histologically confirmed invasive breast cancer that is HER2-positive (IHC3+, and/or ISH positive/amplified) as determined by the local laboratory in accordance with national guidelines
- 3. Has received neoSACT chemotherapy with concomitant trastuzumab and pertuzumab
- 4. pCR (ypT0/is ypN0) in breast and sampled regional lymph nodes as per local pathology

#### reporting

- 5. Imaging of breast and axilla prior to initiation of neoSACT and either:
- 5.1. Breast primary radiological measurement ≤20 mm prior to neoSACT and limited nodal involvement (cN1) confirmed by axillary core biopsy or FNA (cT1N1) OR
- 5.2. Breast primary radiological measurement >20 mm but ≤50 mm and node-negative (cT2N0) or limited nodal involvement (cT2N1)
- 6. Multiple ipsilateral cancers are permitted provided at least one meets the tumour size and axillary node inclusion criteria and none meet any of the exclusion criteria
- 7. Bilateral cancers are permitted provided at least one meets the tumour size and axillary node inclusion criteria and none meet any of the exclusion criteria
- 8. Pre-treatment diagnostic breast tumour biopsy sample available
- 9. Patient must be fit to continue treatment with trastuzumab and have no concomitant medical, psychiatric or social problems that might interfere with informed consent, adherence to the reduced treatment pathway or follow-up
- 10. Provision of written informed consent to participate in HER2-RADICAL

#### Previous inclusion criteria:

- 1. Female or male, age ≥16 years
- 2. Histologically confirmed invasive breast cancer that is HER2-positive (IHC3+, and/or ISH positive/amplified) as determined by the local laboratory in accordance with national guidelines
- 3. Has received neoSACT with a non-anthracycline chemotherapy regimen with at least 3 cycles of concomitant trastuzumab and pertuzumab
- 4. pCR (ypT0/is ypN0) in breast and sampled regional lymph nodes as per local pathology reporting
- 5. Imaging of breast and axilla prior to initiation of neoSACT and either:
- 5.1. Breast primary radiological measurement ≤20 mm prior to neoSACT and limited nodal involvement (cN1) confirmed by axillary core biopsy or FNA (cT1N1) OR
- 5.2. Breast primary radiological measurement >20 mm but ≤50 mm and node-negative (cT2N0) or limited nodal involvement (cT2N1)
- 6. Multiple ipsilateral cancers are permitted provided at least one meets the tumour size and axillary node inclusion criteria and none meet any of the exclusion criteria
- 7. Bilateral cancers are permitted provided at least one meets the tumour size and axillary node inclusion criteria and none meet any of the exclusion criteria
- 8. Pre-treatment diagnostic breast tumour biopsy sample available
- 9. Study consent ≤6 weeks after completing breast cancer surgery
- 10. Patient must be fit to continue treatment with trastuzumab and have no concomitant medical, psychiatric or social problems that might interfere with informed consent, adherence to the reduced treatment pathway or follow-up
- 11. Provision of written informed consent to participate in HER2-RADICAL

### Participant type(s)

Patient

## Healthy volunteers allowed

No

#### Age group

Adult

#### Lower age limit

16 years

#### Sex

All

#### Key exclusion criteria

Current exclusion criteria as of 21/12/2023:

- 1. Evidence of metastatic disease at any time since diagnosis
- 2. Any residual invasive disease following neoSACT. This includes isolated tumour cells in axillary nodes or tissue or evidence of lymphovascular invasion in the breast. Persistent ductal or lobular non-invasive disease (DCIS or LCIS) is permitted. Resection margins must be deemed clear of any residual DCIS according to local MDT protocol
- 3. Breast-conserving primary surgery where it is known that breast irradiation will not be administered (e.g. due to contraindication or patient preference)
- 4. Intraoperative assessment of post-neoSACT axillary SLN using one-stop nucleic acid amplification (OSNA)
- 5. Any planned further resectional surgery for breast cancer (including re-excision, mastectomy, or axillary surgery)
- 6. HER2-negative invasive breast carcinoma
- 7. Breast cancer with clinical stage of T≥3 at diagnosis
- 8. Evidence of scarring (or other pathological features consistent with previous malignant involvement) in >4 axillary nodes or clinical nodal stage  $N\geq 2$  at any time9. Positive SLNB preneoadjuvant systemic therapy as this precludes determination of pCR
- 10. Pregnant and/or lactating women
- 11. Female patient of child-bearing potential, unwilling to use an effective form of contraception during trastuzumab treatment and for 7 months after their last dose of trastuzumab
- 12. Previous diagnosis of invasive breast carcinoma
- 13. Previous diagnosis of any other (non-breast) malignancy unless disease-free for at least 5 years and considered to be at low risk of recurrence or treated basal cell or localised squamous cell carcinoma of the skin or cervical intraepithelial neoplasia
- 14. Chemotherapy administered following surgery (NB. Pertuzumab and/or trastuzumab may have been continued after surgery as per local practice prior to study entry)
- 15. Has received >9 cycles trastuzumab. In the event a patient has received 9 cycles prior to study entry then consent must occur within 3 weeks of the last dose of trastuzumab.
- 16. Clinically significant cardiac disease within 12 months of starting trastuzumab, including unstable angina, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure, cerebral vascular accident, or cardiac arrhythmia associated with haemodynamic instability
- 17. Left ventricular ejection fraction (LVEF) less than 50% on most recent cardiac imaging
- 18. History of interstitial lung disease
- 19. Any medical or other contra-indication to continuing trastuzumab

#### Previous exclusion criteria:

- 1. Evidence of metastatic disease at any time since diagnosis
- 2. Any residual invasive disease following neoSACT. This includes isolated tumour cells in axillary nodes or tissue or evidence of lymphovascular invasion in the breast. Persistent ductal or lobular non-invasive disease (DCIS or LCIS) is permitted. Resection margins must be deemed clear of any residual DCIS according to local MDT protocol
- 3. Any planned further resectional surgery for breast cancer (including re-excision, mastectomy, or axillary surgery)

- 4. HER2-negative invasive breast carcinoma
- 5. Breast cancer with clinical stage of T≥3 at diagnosis
- 6. Evidence of scarring (or other pathological features consistent with previous malignant involvement) in >4 axillary nodes or clinical nodal stage N≥2 at any time
- 7. Positive SLNB pre-neoadjuvant systemic therapy as this precludes determination of pCR
- 8. Pregnant and/or lactating women
- 9. Female patient of child-bearing potential, unwilling to use an effective form of contraception during trastuzumab treatment and for 7 months after their last dose of trastuzumab
- 10. Previous diagnosis of invasive breast carcinoma
- 11. Previous diagnosis of any other (non-breast) malignancy unless disease-free for at least 5 years and considered to be at low risk of recurrence or treated basal cell or localised squamous cell carcinoma of the skin or cervical intraepithelial neoplasia
- 12. Chemotherapy administered following surgery (NB. Pertuzumab and/or trastuzumab may have been continued after surgery as per local practice prior to study entry)
- 13. Has received >9 cycles trastuzumab
- 14. Any medical or other contra-indication to continuing trastuzumab

## Date of first enrolment 03/12/2021

Date of final enrolment 30/11/2027

## Locations

## Countries of recruitment

**United Kingdom** 

England

Northern Ireland

Scotland

G12 0XH

Wales

Study participating centre Gartnavel Royal Hospital 1055 Great Western Road Glasgow United Kingdom

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place

Edinburgh United Kingdom EH1 3EG

## Study participating centre Belfast City Hospital

Lisburn Road Belfast United Kingdom BT9 7AB

## Study participating centre Royal Sussex County Hospital

Eastern Road Brighton United Kingdom BN2 5BE

### Study participating centre The Maidstone Hospital

Hermitage Lane Maidstone United Kingdom ME16 9QQ

## Study participating centre Royal Free Hospital

Pond Street London United Kingdom NW3 2QG

## Study participating centre Queens Medical Centre

Derby Road Nottingham United Kingdom NG7 2UH

## Study participating centre Yeovil District Hospital

Higher Kingston Yeovil United Kingdom BA21 4AT

### Study participating centre Colchester Dist General Hospital

Turner Road Colchester United Kingdom CO4 5JL

### Study participating centre Ysbyty Gwynedd

Penrhosgarnedd Bangor United Kingdom LL57 2PW

## Study participating centre NHS Forth Valley

33 Spittal Street Stirling United Kingdom FK8 1DX

## Study participating centre Royal Cornwall Hospital

Treliske Truro United Kingdom TR1 3LJ

## Study participating centre Poole Hospital

Longfleet Road Poole United Kingdom BH15 2JB

#### Study participating centre Kent & Canterbury Hospital

Ethelbert Road Canterbury United Kingdom CT1 3NG

## Study participating centre St Thomas' Hospital

Westminster Bridge Road London United Kingdom SE1 7EH

#### Study participating centre Christie Hospital

550 Wilmslow Road Withington Manchester United Kingdom M20 4BX

## Study participating centre Medway Maritime Hospital

Windmill Road Gillingham United Kingdom ME7 5NY

## Study participating centre NHS Borders

Newstead Melrose United Kingdom TD6 9DB

#### Study participating centre

#### Queen Elizabeth Hospital

Gayton Road King's Lynn United Kingdom PE30 4ET

## Study participating centre St Mary's Hospital

South Wharf Road London United Kingdom W2 1BL

## Study participating centre Worcestershire Royal Hospital

Charles Hastings Way Worcester United Kingdom WR5 1DD

### Study participating centre Northern General Hospital

Herries Road Sheffield United Kingdom S5 7AU

## Study participating centre Beatson West of Scotland Cancer Centre

1053 Great Western Road Glasgow United Kingdom G12 0YN

## Study participating centre Royal Bournemouth Hospital

Castle Lane East Bournemouth United Kingdom BH7 7DW

## Study participating centre William Harvey Hospital

Kennington Road Willesborough Ashford United Kingdom TN24 0LZ

## Study participating centre Queen Elizabeth the Queen Mother Hospital

St. Peters Road Margate United Kingdom CT9 4AN

#### Study participating centre Nottingham City Hospital

Hucknall Road Nottingham United Kingdom NG5 1PB

#### Study participating centre Charing Cross Hospital

Fulham Palace Road London United Kingdom W6 8RF

## Study participating centre Bristol Haematology and Oncology Center

22 Horfield Rd Bristol United Kingdom BS2 8ED

## Study participating centre Peterborough City Hospital

Edith Cavell Campus

Bretton Gate Bretton Peterborough United Kingdom PE3 9GZ

## Study participating centre Dumfries & Galloway Royal Infirmary

Cargenbridge
Dumfries
Dumfries and Galloway
United Kingdom
DG2 8RX

### Study participating centre Royal Lancaster Infirmary

Ashton Road Lancaster United Kingdom LA1 4RP

## Study participating centre Westmorland General Hospital

Burton Rd Kendal United Kingdom LA9 7RG

### Study participating centre Furness General Hospital

Dalton Lane Barrow-in-furness United Kingdom LA14 4LF

## Study participating centre Clatterbridge Cancer Centre

65 Pembroke PLACE Liverpool United Kingdom L7 8YA

## Study participating centre St Mary's Hospital

St. Marys Hospital Parkhurst Road Newport United Kingdom PO30 5TG

## Study participating centre Glan Clwd Hospital

Ysbyty Glan Clwydd Bodelwyddan Rhyl United Kingdom LL18 5UJ

## Study participating centre Wrexham Maelor Hospital

Croesnewydd Road Wrexham Technology Park Wrexham United Kingdom LL13 7TD

## Study participating centre Weston Park Hospital

Whitham Rd Broomhall Sheffield United Kingdom S10 2SJ

## Study participating centre Aberdeen Royal Infirmary

Foresterhill Road Aberdeen United Kingdom AB25 2ZN

## Study participating centre West Middlesex University Hospital

Twickenham Road Isleworth United Kingdom TW7 6AF

## Study participating centre Weston General Hospital

Grange Road Uphill Weston-super-mare United Kingdom BS23 4TQ

## Study participating centre Uclh

250 Euston Road London United Kingdom NW1 2PQ

## Study participating centre Royal Devon and Exeter Hospital

Royal Devon & Exeter Hospital Barrack Road Exeter United Kingdom EX2 5DW

#### Study participating centre Maidstone

Maidstone Hospital Hermitage Lane Maidstone United Kingdom ME16 9QQ

### Study participating centre

#### Northampton General Hospital

Cliftonville Northampton United Kingdom NN1 5BD

## Sponsor information

#### Organisation

Institute of Cancer Research

#### **ROR**

https://ror.org/043jzw605

## Funder(s)

#### Funder type

Government

#### **Funder Name**

NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: .

## **Results and Publications**

### Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study will be available on request from the HER2-RADICAL trial team via her2radical-icrctsu@icr.ac.uk via completion of a data access request form after such time that the primary analysis publication and any other key analyses have been completed. Optional advanced consent/authorisation for the possible future sharing of information collected about patients will be obtained at study entry.

## IPD sharing plan summary

Available on request

### **Study outputs**

| Output type                   | Details                       | Date created | Date added | Peer reviewed? | Patient-facing? |
|-------------------------------|-------------------------------|--------------|------------|----------------|-----------------|
| HRA research summary          |                               |              | 28/06/2023 |                | No              |
| Participant information sheet | Participant information sheet | 11/11/2025   | 11/11/2025 | No             | Yes             |
| <u>Protocol file</u>          | version 2.0                   | 11/10/2021   | 16/05/2022 | No             | No              |
| Protocol file                 | version 4.0                   | 24/02/2023   | 21/12/2023 | No             | No              |