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A trial looking at buparlisib for HER2 positive breast cancer that has spread to the brain

Submission date 30/01/2017	**Recruitment status** Stopped	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 31/01/2017	**Overall study status** Stopped	
Last Edited 13/07/2018	**Condition category** Cancer	

Plain English summary of protocol
Lay summary under review by external organisation

Contact information

Type(s)
Public

Contact name
Miss Helen Scott

Contact details
Cancer Research UK Liverpool Cancer Trials Unit
Block C, Waterhouse Building
1-3 Brownlow Street
Liverpool
United Kingdom
L69 3GL
+44 (0)151 794 8209
hscott@liv.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2015-003103-27

Protocol serial number
20750

Study information

Scientific Title
A proof of concept phase II study of Buparlisib in HER2 positive breast cancer with brain metastasis following HER2 directed monoclonal antibody therapy

Acronym
BLUEBELL

Study objectives
The aim of this study is to evaluate the effects of two-weeks preoperative therapy with buparlisib in women with previously confirmed HER2-positive breast cancer with newly diagnosed brain metastasis following HER2-directed antibody therapy and who are considered a candidate for brain resection surgery.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Haydock Research Ethics Committee, 22/02/2016, ref: 16/NW/0066

Study design
Non-randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Cancer, Primary sub-specialty: Breast Cancer

Interventions
All patients enrolled on the trial will receive the study drug buparlisib. Patients will take 100mg of buparlisib once daily until the day before scheduled neurosurgery. Neurosurgery will be scheduled 15-18 days from commencing treatment, and so patients will take the study treatment for 14-17 days.

After patients have completed 14-17 days treatment, they will receive scheduled surgery one day later (day 15-17).

After this, patients will return 14 days post-surgery and the following procedures will be carried out at this visit:
1. Physical Examination
2. Vital signs
3. ECOG performance status
4. Haematology and clinical biochemistry
5. HbA1c
6. Mood questionnaires
7. Review/recording of concomitant medications
8. Assessment & recording of adverse events

Following this, patients will return again on Day 42, and the following procedures will be carried out:
1. Mood questionnaires
2. Review/recording of concomitant medications
3. Assessment & recording of adverse events

Adverse events will be recorded until 30 days post treatment.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
"Response" to buparlisib, defined as a 25% or greater reduction in FLT uptake after 14 days of treatment, measured using FLT-PET scans at baseline and 14 days.

Key secondary outcome(s))
1. Difference between Intratumoral and serum buparlisib concentrations, measured using tumour and serum samples taken at the time of surgery
2. Difference between cerebrospinal fluid and serum buparlisib concentrations, measured using cerebrospinal fluid/serum samples taken at the time of surgery
3. Ki67 proliferation index, within resected brain metastasis following buparlisib, measured using tumour samples taken at the time of surgery
4. Presence or absence of PIK3CA mutations in cell free DNA as measured by the changes in FLT uptake by PET scanning at baseline and 14 days
5. Presence or absence of PIK3CA mutations in cell free DNA as measured by the changes in FLT uptake by PET scanning at baseline and 14 days
6. Size of brain metastasis as assessed by MRI with gadolinium contrast enhancement at baseline and 14 days
7. Occurrence of SAEs and toxicities according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v 4.03), measured using SAEs & AEs recorded from registration to 30 days post treatment, and mood questionnaires at baseline, 7, 14, 28 and 42 days

Completion date
10/10/2019

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. Female 16 years or above
2. Histologically confirmed HER2-positive breast cancer (immunohistochemistry 3+ or

fluorescence in situ hybridization with an amplification ratio ≥2.0)
3. Newly diagnosed brain metastasis
4. At least one brain metastasis measuring ≥2.5cm (to minimise partial volume effects in PET imaging and quantification)
5. Previous treatment with Trastuzumab with or without Pertuzumab either in the adjuvant or metastatic setting
6. Discussed with neuro-oncology MDT and considered a candidate for macroscopic resection
7. ECOG performance status 0 to 2
8. Patient has adequate bone marrow and organ function as defined by the following laboratory values:
8.1. Absolute Neutrophil Count (ANC) > 1.0 x 109/L
8.2. Platelets (plt) >100 x 109/L
8.3. Haemoglobin (Hgb) ≥ 9 g/dl
8.4. INR ≤ 1.5
8.5. Potassium, calcium (corrected for serum albumin) and magnesium within normal limits
8.6. Serum creatinine ≤ 1.5 x ULN
8.7. Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) within normal range (or < 3.0 x ULN if liver metastases are present)
8.8. Total serum bilirubin within normal range (or ≤ 1.5 x ULN if liver metastases are present; or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal range in patients with well documented Gilbert's Syndrome, which is defined as presence of several episodes of unconjugated hyperbilirubinemia with normal results from Cells Blood Count (CBC), including normal reticulocyte count and blood smear, normal liver function test results, and absence of other contributing disease processes at the time of diagnosis
8.9. Alkaline phosphatase ≤ 5 x upper limit of normal, unless bone metastases in the absence of liver disease
8.10. Fasting plasma glucose ≤ 120 mg/dL or 6.7 mmol/L
8.11. HbA1c ≤ 8 % (≤ 64mmol/mol)
9. Left ventricular Ejection Fraction (LVEF) > 50 % as determined echocardiogram
10. Life expectancy > 3 months
11. Ability to swallow and retain oral medication
12. Written informed consent, able to comply with treatment and follow up

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Prior treatment with Lapatinib or other HER2-directed tyrosine kinase inhibitor (given such patients will have already received some form of local therapy)
2. Cystic brain metastasis with minimal solid component (defined on MRI)
3. Prior treatment with either a P13K or AKT inhibitor
4. Receiving treatment with other antineoplastic agents (except for HER2-directed monoclonal

antibody therapy)
5. Treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated before enrollment, may be continued.
5. Wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered to grade 1 or better from related side effects of such therapy (exceptions include alopecia, bone marrow and organ functions)
6. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects
7. Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g. risk of doing harm to self or others), or patients with active severe personality disorders (defined according to DSM- IV). For patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug. For patients receiving psychotropic treatments at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug.
8. GAD-7 mood scale ≥ 15
9. A score ≥ 12 on the PHQ-9 questionnaire
10. Selection of response “1, 2 or 3” to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9)
11. CTCAE grade 3 anxiety
12. Patient has active cardiac disease or a history of cardiac dysfunction including any of the following:
12.1. Unstable angina pectoris within 6 months prior to study entry
12.2. Symptomatic pericarditis
12.3. Documented myocardial infarction within 6 months prior to study entry
12.4. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
12.5. Documented cardiomyopathy
13. QTcF > 480 msec on the screening ECG (using the QTcF formula)
14. Currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to registration.
15. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of buparlisib
16. Prior malignancies (other than breast cancer) within the last 5 years, except for adequately treated in situ carcinoma of the cervix or basal cell/squamous cell carcinoma of the skin
17. Currently receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed
18. Current treatment with drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A. Such agents must be discontinued for at least one week prior to starting treatment
19. History of non-compliance to medical regimen
20. Acute viral hepatitis or a history of chronic or active HBV or HCV infection, (typically defined by elevated AST/ALT (persistent or intermittent), high HBV DNA level, HBsAg positive, or high HCV RNA level (testing not mandatory)
21. Known history of HIV infection infection (testing not mandatory)
22. Other serious uncontrolled medical conditions or concurrent medical illness
23. Pregnant, lactating or potentially childbearing women not using adequate contraception
24. Adequate contraception is defined as either:

24.1. Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
24.2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
24.3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female study subjects, the vasectomized male partner should be the sole partner for that patient.

Date of first enrolment
10/04/2017

Date of final enrolment
10/04/2019

Locations

Countries of recruitment
United Kingdom

England

Scotland

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

Study participating centre
The Walton Centre
Lower Lane
Fazakerley
Liverpool
United Kingdom
L9 7LJ

Study participating centre
Clatterbridge Cancer Centre
Clatterbridge Road
Wirral

United Kingdom
CH63 4JY

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Queen Alexandra Hospital
Southwick Hill Road
Cosham
United Kingdom
PO6 3LY

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

Study participating centre
The Queen Elizabeth University Hospital
1345 Govan Road
Govan
Glasgow
United Kingdom
G51 4TF

Study participating centre
Salford Royal Hospital
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
St Thomas' Hospital
Westminster Bridge Road
Lambeth
London
United Kingdom
SE1 7EH

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

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
Novartis Pharmaceuticals UK Limited

Alternative Name(s)
Novartis UK, NOVARTIS UK LIMITED

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made 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			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes