Clinical trial results:
A randomised phase II screening trial with functional imaging and patient reported toxicity sub-studies comparing LApatiNib plus capecitabine versus continued Trastuzumab plus capecitabine after local therapy in patients with ERb B2 positive metastatic breast cancer developing braiN metastasis /es

Summary

EudraCT number	2010-022737-28
Trial protocol	GB
Global end of trial date	13 May 2014

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	29 July 2015
Summary attachment (see zip file)	End of trial report (LANTERN End of Trial Report v1 0 22042015.pdf)

Trial information

Trial identification

Sponsor protocol code	CO10/9344

Additional study identifiers

ISRCTN number	ISRCTN58771616
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Leeds Teaching Hospitals NHS Trust
Sponsor organisation address	Beckett Street Leeds, Leeds, United Kingdom, LS9 7TF
Public contact	QA department, Leeds Institute of Clinical Research, ctruq@leeds.ac.uk
Scientific contact	QA department, Leeds Institute of Clinical Research, ctruq@leeds.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2014
Global end of trial reached?	Yes
Global end of trial date	13 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of lapatinib plus capecitabine compared with trastuzumab plus capecitabine on time to progression of central nervous system (CNS) metastases as measured by RECIST.

Protection of trial subjects:

Inclusion/Exclusion:
Eligibility criteria were designed with patient safety as a primary concern and therefore no one is unfairly excluded from
or included in the trial.

Consent:
Patients will be provided with written information about the trial and verbal information from a member of the local research team. Informed consent will be taken by an authorised clinically and GCP trained member of staff who will ensure that the person understands the purpose and nature of the study and what it involves, the benefits, risks and burdens and the alternative treatments available. They will also ensure the patient is able to retain the information long enough to make an effective decision with free choice.

Risk burdens and benefits:
Patients will be exposed to some additional risks. Patients have a risk of drug toxicity with both treatment arms.
Patients will also undergo MRI scans. Additional hospital visits for treatment, clinical review and investigations could
inconvenience patients. Benefit of inclusion include potential clinical response with either treatment arm. The
LANTERN trial will add to the evidence base for treatment options in this group and may lead to a phase III trial.

Confidentiality:
All information collected during the course of the trial will be kept strictly confidential. Information will be held securely
on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the
1998 Data Protection Act.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

109 patients were screened. 34 were registered and 75 excluded due to: ineligibility (57), patient declined (7), patient too ill to consent (1), lapatinib given off trial (3), and other reason (7). The 4 registered patients were not randomised due to: ineligibility (2), patient choice (1), clinician choice (1).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lapatinib + Capecitabine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lapatinib 1250mg daily

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 twice daily days 1-14

21 day cycle

Arm title	Trastuzumab + Capecitabine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6mg/kg 3-weekly

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1250 mg/m2 twice daily. Day 1-14

Number of subjects in period 1	Lapatinib + Capecitabine	Trastuzumab + Capecitabine
Started	16	14
Completed	5	6
Not completed	11	8
Consent withdrawn by subject	1	1
Adverse event, non-fatal	3	1
Death	-	1
Lack of efficacy	7	5

Baseline characteristics

Reporting groups	
Reporting group title	Lapatinib + Capecitabine
Reporting group description: -	
Reporting group title	Trastuzumab + Capecitabine
Reporting group description: -	

Reporting group values	Lapatinib + Capecitabine	Trastuzumab + Capecitabine	Total
Number of subjects	16	14	30
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	12	27
From 65-84 years	1	2	3
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	16	14	30
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Final
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Analyses was conducted on the intention-to-treat (ITT) population, where participants were included according to the treatment arm they were randomised to regardless of whether they prematurely discontinued the treatment or did not comply with the regimen. The intention-to-treat (ITT) population therefore included all 30 randomised participants, and was the same as the Safety population as all participants received at least one dose of study drug.

Reporting group values	Final		
Number of subjects	30		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	27		
From 65-84 years	3		
85 years and over	0		
Gender categorical Units: Subjects			
Female	30		
Male	0		

End points

End points reporting groups

Reporting group title	Lapatinib + Capecitabine
Reporting group description: -	
Reporting group title	Trastuzumab + Capecitabine
Reporting group description: -	
Subject analysis set title	Final
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Analyses was conducted on the intention-to-treat (ITT) population, where participants were included according to the treatment arm they were randomised to regardless of whether they prematurely discontinued the treatment or did not comply with the regimen. The intention-to-treat (ITT) population therefore included all 30 randomised participants, and was the same as the Safety population as all participants received at least one dose of study drug.

Primary: CNS progression-free survival

End point title	CNS progression-free survival

End point description:

Time to progression of CNS metastases was defined as time from randomisation to the date of progression confirmed by:
- Cranial MRI scans (RECIST v1.1)
- Local standard clinical practice where an MRI scans was not performed (i.e. clinical/other radiological evidence)

Participants missing follow-up data, or alive and CNS progression free at the time of analysis, were censored at the date last known to be alive and progression-free. Participants with disease progression confirmed during their 24 week follow up assessment whose assessment fell outside of the 2 week window were included as having disease progression on their assessment date. Participants still receiving treatment following the final 24 week assessment, for whom it was subsequently reported that they discontinued treatment due to CNS disease progression (after the 24 week assessment) were censored at the last date they were known to be alive and CNS progression-free (date of 24 week assessment).

End point type	Primary

End point timeframe:

24 week trial follow up period.
Participants with disease progression confirmed during their 24 week follow up assessment whose assessment fell outside of the 2 week window were included as having disease progression on their assessment date.

End point values	Lapatinib + Capecitabine	Trastuzumab + Capecitabine	Final	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16	14	30	
Units: Patients with CNS disease progression				
CNS progression	8	6	14	

Statistical analyses

Statistical analysis title	CNS progression-free survival

Statistical analysis description:

Analyses, unless otherwise stated, were based upon summary and descriptive statistics only.
Survival curves for CNS progression-free survival were calculated using the Kaplan Meier method and an unadjusted analysis was conducted using a two-sided log-rank test to assess the difference between the treatment arms.

Comparison groups	Lapatinib + Capecitabine v Trastuzumab + Capecitabine
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.8093 [2]
Method	Log-rank

Notes:

[1] - CNS disease progression was reported in 14 (46.7%) participants during their 24 week trial follow up period: 8 (50%) lapatinib plus capecitabine participants and 6 (42.9%) trastuzumab plus capecitabine participants.
Accounting for participants censored before and after 24 weeks, the Kaplan Meier estimate of CNS progression-free survival at 24 weeks was 58.2% (95% CI: 32.5%, 83.9%) in the lapatinib plus capecitabine arm and 58.8% (95% CI: 30.4%, 87.2%) in the trastuzumab plus capecitabine arm.
[2] - The number of randomised participants was insufficient to detect any meaningful differences in time to disease progression between participants in the arms.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All AEs, evaluated according to NCI-CTCAE v4.0m were collected 3 weekly during trial treatment up to 24weeks.
SAEs were reported from randomisation to 30 days after the 24 week clinical review visit.

Adverse event reporting additional description:

The SAE active monitoring period is from randomised to 30 days after the 24 week clinical review visit. If a participant continues to receive trial treatment after the 24 week clinical review visit, SARS and SUSARs are reported until the end of trial.

Assessment type	Systematic

Dictionary used

Dictionary name	body system coding
Dictionary version	1

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: See attached End of Trial Report submitted to the MHRA in April 2015 for details of adverse events. Leeds Institute of Clinical Trials Research is an academic trials unit where full MedDRA coding is not the standard. It has therefore not been possible for adverse event data to be accurately entered into the full data view within EudraCT as all mandatory categories cannot be completed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2011	Change of timing of QoL & Patient self-reported symptoms and side effects assessment. Clarification to eligibility criteria for previous treatment with trastuzumab Addition of option of MUGA scans Addition of potential interactions between capecitabibe and other medication Amendment to haematological toxicities for clarification of inconsistencies and unnecessary information within the protocol Amendment to advice on trastuzumab delay of over 2 weeks for clarification of inconsistencies within protocol Update to timing of protocol defined schedule of events Update to assessments required prior to each treatment cycle (3 weekly) Addition of alternative location for patient interviews as clinic visits may not always be suitable for the patient.
19 April 2011	Addition of PK sampling sub-study Correction to consent form statements
19 May 2011	Addition of PK sampling sub-study Amendment to eligibility criteria to include amiodarone as an inclusion criteria and removal of this drug from concomitant therapy section. Update to exclusion criteria to clarify prior treatment with capecitabine in the metastaic setting is an exclusion criteria Update to permitted dose modifications of lapatinin cececitabine following discussions with LANTERN investigators Removal of requirement for as assessment of disease progression at 3 weekly treatment visits to clarify this is only necessary at 12 & 24 weeks post randomisation follow up visits.
16 August 2011	Amendment to eligibility criteria to amend the definition of normal organ and bone marrow function and to remove this from the exclusion criteria. Clarification of pre-treatment investigations, concomitant therapy and dosing and frequency of treatment in section 9 of the protocol. Amendment to instructions for lapatinib and capecitabine dose modifications following adverse events Update to schedule of events to remove laboratory investigations.
08 February 2012	Update to PIS/protocol to include a statement that if informed consent is obtained from the participant and the participant subsequently becomes unable to provide on-going informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid. Participants who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the Principal Investigator and participants care/ family with the participants best interests foremost in the decision making process. On going collection of safety and follow up data will continue via clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trials intention to treat analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

28 March 2013	The timeframe for trastuzumab treatment was expanded from current only, to current, or prior (in the adjuvant or metastatic setting) treatment. The requirement for patients to have developed brain metastases whilst on trastuzumab treatment was also been removed. Eligibility criteria was expanded to include not only newly diagnosed brain metastases, but also progression of CNS metastases within the last 12 months. Clarified SARs / SUSARs will continue to be reported after 24 weeks for patients still on trial treatment. SAE collection to start from randomisation not registration. Pregnancies will be followed up until outcome is known. A number of new stratification factors added such as: •Type of local therapy (this has been expanded to include both types of therapy) •Timeframe of trastuzumab treatment and which setting (metastatic / adjuvant or both) •Timeframe of diagnosis of brain metastases / progression of brain metastases Treatment allocation section updated to reflect change of randomisation from stratified permuted block randomisation to minimisation. Update to Trastuzumab preparation & IMP Formulation and Storage. Some trial sites store reconstituted trastuzmab out of line with the SPC. Trastuzumab dose section updated to state that dose banding is permitted. Clarified guidance to be followed if a loading dose is required. Updated to state that in the case of a treatment delay future treatment is at the investigation of the investigator Trastuzumab dose section updated to state that dose banding is permitted. Clarified guidance to be followed if a loading dose is required. Updated to state that in the case of a treatment delay future treatment is at the investigation of the investigator. Redefined end of trial as 30 days after 24 week clinical rereview or 30 days after last lapatinib trial treatment administered (whichever date is later)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported