



Clinical trial results: Effect of Perioperative AntiHER2 Therapy on Early Breast Cancer Study - Biological Phase

Summary

EudraCT number	2008-005466-30
Trial protocol	GB
Global end of trial date	19 December 2022

Results information

Result version number	v1 (current)
This version publication date	03 January 2024
First version publication date	03 January 2024

Trial information

Trial identification

Sponsor protocol code	CCR3104
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Additional study identifiers

ISRCTN number	ISRCTN15004993
ClinicalTrials.gov id (NCT number)	NCT01104571
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research
Sponsor organisation address	Cotswold Road, Sutton, United Kingdom, SM2 5NG
Public contact	Trial Manager- EPHOS-B trial, Trial Manager- EPHOS-B trial, 44 2087224349, ephos-b-icrctsu@icr.ac.uk
Scientific contact	Trial Manager- EPHOS-B trial, Trial Manager- EPHOS-B trial, 44 2087224349, ephos-b-icrctsu@icr.ac.u
Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Southmoor Road, Manchester, United Kingdom, M23 9LT
Public contact	Research and Development Manager, Manchester University NHS Foundation Trust, 44 01612914045,
Scientific contact	Research and Development Manager, Manchester University NHS Foundation Trust, 44 0161 291 4045,
Sponsor organisation name	University of Manchester
Sponsor organisation address	Brunswick Street, Manchester, United Kingdom, M13 9PL
Public contact	Research and Development Manager, University of Manchester, 44 01612752728, clinicaltrials@manchester.ac.uk
Scientific contact	Nigel Bundred, University of Manchester, 44 0161 275 2725, clinicaltrials@manchester.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	19 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2020
Global end of trial reached?	Yes
Global end of trial date	19 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The Effect of Perioperative Anti-HER2 therapy on Early Breast Cancer Study – Biological phase (EPHOS-B) was designed to assess whether either single-agent lapatinib or trastuzumab given as perioperative treatment had effects on Ki67 and/or apoptosis compared with no anti-HER2 therapy prior to surgery (part 1). Emerging evidence from the NeoSphere trial on the safety and efficacy of combination anti-HER2 therapy led to a protocol amendment, enabling patient allocation between control, trastuzumab alone, or the combination of lapatinib and trastuzumab (part 2).

Therefore, the main aim is to determine whether pre-operative treatment of HER2 positive breast cancer patients with anti HER2 therapy increases cell death and/or decreases proliferation.

Protection of trial subjects:

Patients had to be willing to undergo adjuvant chemotherapy and trastuzumab postsurgery as per standard of care and provide written informed consent for participation and donation of tissue and blood samples. Patients with significant cardiac abnormalities were ineligible. Baseline left ventricular ejection fraction (LVEF) $\geq 55\%$ was required for trial entry. The trial was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki.

Background therapy:

The human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor amplified or overexpressed in 15% to 20% of breast cancers. HER2 lacks a specific ligand, and signaling occurs after the formation of heterodimers with HER1 and HER3 (1). Targeting this pathway improves outcomes for patients with HER2-positive breast cancer.

Evidence for comparator:

Trastuzumab interacts with the extracellular domain of the HER2 protein to inhibit its function, but the mechanism of action is incompletely understood. Lapatinib blocks the HER1/2 internal tyrosine kinase domain and inhibits proliferation of HER2-positive cancers as shown in a small preoperative trial. Changes in proliferation biomarkers, including Ki67, predict clinical response and long-term outcome after 2 weeks of endocrine therapy in estrogen receptor (ER)-positive breast cancer. Incompletely excised breast cancers requiring re-excision within 48 days of surgery showed a significant increase in proliferation if they were HER2-positive, but not if they were HER2-negative. Preventing these early changes provides a rationale for window-of-opportunity studies investigating response to short-term treatment, enhancing prospects for personalizing medicine by identifying tumors sensitive to anti-HER2 therapy (without added chemotherapy).

Actual start date of recruitment	15 November 2010
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: 257
Worldwide total number of subjects	257
EEA total number of subjects	0

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)	210
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

257 patients were recruited from 21 UK centers; 130 entered part 1 between November 15, 2010, and July 29, 2013, and 127 entered part 2 between August 6, 2013 and September 10, 2015. The main results of the trial were presented after a median follow-up was 6 years (IQR, 5.2–7.4), and published in 2022 (See links below).

Pre-assignment

Screening details:

Patients that met the eligibility criteria were recruited into the study. In short, newly diagnosed women with HER2-positive invasive breast cancer due to undergo surgery within 28 days. Patients had to be willing to undergo adjuvant chemotherapy and trastuzumab postsurgery as per standard of care. Baseline LVEF >=55% was required.

Period 1

Period 1 title	EPHOS-B Part 1&2 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 - Trastuzumab

Arm description:

Peri-operative trastuzumab, starting 11 days (+2 or -1day) prior to surgery on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery

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

Dosage and administration details:

Pre-operative 6mg/kg given iv days 1 & 8 (accelerated dosing) commencing 11 days pre-surgery (+2 or -1 day).

After surgery, 2mg/kg on Day 15 -19

Arm title	Part 1 - Lapatinib
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Arm description:

Lapatinib for 28 days commencing 11 days (+2 or -1day) prior to surgery

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:

1500 mgs daily (6 tablets of 250mg) for 28 days, to be taken all in one single dose

Arm title	Part 1 - Control
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Arm description:

No perioperative treatment

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Part 2 - Trastuzumab
Arm description:	
Peri-operative trastuzumab, starting 11 days (+2 or -1day) prior to surgery on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery	
Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Pre-operative 6mg/kg given iv days 1 & 8 (accelerated dosing) commencing 11 days pre-surgery (+2 or -1 day).	
After surgery, 2mg/kg on Day 15 -19	
Arm title	Part 2 - Combination
Arm description:	
Peri-operative treatment, starting 11 days (+2 or -1day) prior to surgery:	
- Trastuzumab, on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery	
- Lapatinib for 28 days commencing 11 days (+2 or -1day) prior to surgery	
Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Pre-operative 6mg/kg given iv days 1 & 8 (accelerated dosing) commencing 11 days pre-surgery (+2 or -1 day).	
After surgery, 2mg/kg on Day 15 -19	
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
1000 mgs daily (4 tablets of 250mg) for 28 days, to be taken all in one single dose	
Arm title	Part 2 - Control
Arm description:	
No perioperative treatment	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control
Started	57	51	22
Completed	55	49	22
Not completed	2	2	0
Consent withdrawn by subject	1	2	-
Protocol deviation	1	-	-

Number of subjects in period 1	Part 2 - Trastuzumab	Part 2 - Combination	Part 2 - Control
Started	32	66	29
Completed	32	65	28
Not completed	0	1	1
Consent withdrawn by subject	-	-	-
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups

Reporting group title	Part 1 - Trastuzumab
Reporting group description: Peri-operative trastuzumab, starting 11 days (+2 or -1day) prior to surgery on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery	
Reporting group title	Part 1 - Lapatinib
Reporting group description: Lapatinib for 28 days commencing 11 days 11 days (+2 or -1day) prior to surgery	
Reporting group title	Part 1 - Control
Reporting group description: No perioperative treatment	
Reporting group title	Part 2 - Trastuzumab
Reporting group description: Peri-operative trastuzumab, starting 11 days (+2 or -1day) prior to surgery on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery	
Reporting group title	Part 2 - Combination
Reporting group description: Peri-operative treatment, starting 11 days (+2 or -1day) prior to surgery: - Trastuzumab, on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery - Lapatinib for 28 days commencing 11 days 11 days (+2 or -1day) prior to surgery	
Reporting group title	Part 2 - Control
Reporting group description: No perioperative treatment	

Reporting group values	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control
Number of subjects	57	51	22
Age categorical Units: Subjects			
<35	2	0	0
35-49	27	24	5
50-59	12	15	10
60-69	11	11	6
70-79	5	1	1
>=80	0	0	0
Gender categorical Units: Subjects			
Female	57	51	22
Male	0	0	0
Menopausal Status Units: Subjects			
Pre-menopausal	24	21	4
Peri-menopausal	33	30	18
Grade Units: Subjects			
Grade 1	3	0	0
Grade 2	20	21	9
Grade 3	28	24	13
Unknown	6	6	0

Tumour size (cm)			
Units: Subjects			
<2cm	26	21	11
2-5cm	25	27	10
>=5cm	6	3	1
ER status			
Units: Subjects			
Negative	20	20	7
Positive	37	31	15
PgR status			
Units: Subjects			
Negative	20	23	8
Positive	21	17	6
Missing	16	11	8

Reporting group values	Part 2 - Trastuzumab	Part 2 - Combination	Part 2 - Control
Number of subjects	32	66	29
Age categorical			
Units: Subjects			
<35	1	1	1
35-49	10	19	8
50-59	17	22	9
60-69	4	20	7
70-79	0	3	4
>=80	0	1	0
Gender categorical			
Units: Subjects			
Female	32	66	29
Male	0	0	0
Menopausal Status			
Units: Subjects			
Pre-menopausal	11	25	9
Peri-menopausal	21	41	20
Grade			
Units: Subjects			
Grade 1	0	2	0
Grade 2	14	26	13
Grade 3	17	36	14
Unknown	1	2	2
Tumour size (cm)			
Units: Subjects			
<2cm	19	39	18
2-5cm	13	26	11
>=5cm	0	1	0
ER status			
Units: Subjects			
Negative	11	15	12
Positive	21	51	17
PgR status			
Units: Subjects			
Negative	16	28	17

Positive	8	18	5
Missing	8	20	7

Reporting group values	Total		
Number of subjects	257		
Age categorical Units: Subjects			
<35	5		
35-49	93		
50-59	85		
60-69	59		
70-79	14		
>=80	1		
Gender categorical Units: Subjects			
Female	257		
Male	0		
Menopausal Status Units: Subjects			
Pre-menopausal	94		
Peri-menopausal	163		
Grade Units: Subjects			
Grade 1	5		
Grade 2	103		
Grade 3	132		
Unknown	17		
Tumour size (cm) Units: Subjects			
<2cm	134		
2-5cm	112		
>=5cm	11		
ER status Units: Subjects			
Negative	85		
Positive	172		
PgR status Units: Subjects			
Negative	112		
Positive	75		
Missing	70		

End points

End points reporting groups

Reporting group title	Part 1 - Trastuzumab
Reporting group description: Peri-operative trastuzumab, starting 11 days (+2 or -1day) prior to surgery on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery	
Reporting group title	Part 1 - Lapatinib
Reporting group description: Lapatinib for 28 days commencing 11 days 11 days (+2 or -1day) prior to surgery	
Reporting group title	Part 1 - Control
Reporting group description: No perioperative treatment	
Reporting group title	Part 2 - Trastuzumab
Reporting group description: Peri-operative trastuzumab, starting 11 days (+2 or -1day) prior to surgery on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery	
Reporting group title	Part 2 - Combination
Reporting group description: Peri-operative treatment, starting 11 days (+2 or -1day) prior to surgery: - Trastuzumab, on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery - Lapatinib for 28 days commencing 11 days 11 days (+2 or -1day) prior to surgery	
Reporting group title	Part 2 - Control
Reporting group description: No perioperative treatment	

Primary: ki67 biological response

End point title	ki67 biological response
End point description: A patient is classed as having had a Ki67 biological response if they have had a relative decrease in Ki67 of >30% between baseline and surgery. Percentage change will be defined as $((\text{surgery score} + 0.1) - (\text{pre-treatment score} + 0.1)) / (\text{pre-treatment score} + 0.1) * 100$.	
End point type	Primary
End point timeframe: From baseline biopsy to surgery (2-weeks approx)	

End point values	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control	Part 2 - Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49 ^[1]	44	22	31
Units: Patients				
Response	18	29	1	14
Non-response	31	15	21	17

Notes:

[1] - Patients who had paired biopsy and surgery ki67 analysis

End point values	Part 2 -	Part 2 - Control		
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	Combination			
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	28		
Units: Patients				
Response	36	2		
Non-response	13	26		

Statistical analyses

Statistical analysis title	Lapatinib vs Control (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Control
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Statistical analysis title	Trastuzumab vs Control (all)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Control v Part 2 - Trastuzumab v Part 2 - Control
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Statistical analysis title	Combination vs Control (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Control
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Statistical analysis title	Combination vs Trastuzumab (Part 2)
Comparison groups	Part 2 - Trastuzumab v Part 2 - Combination

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Fisher exact

Statistical analysis title	Trastuzumab vs Lapatinib (Part 1)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Lapatinib
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Fisher exact

Primary: Apoptosis biological response

End point title	Apoptosis biological response
End point description: A patient is classed as having had an apoptosis biological response if they have had a relative increase in apoptosis of >30% between baseline and surgery. Percentage change will be defined as $((\text{surgery score} + 0.1) - (\text{pre-treatment score} + 0.1)) / (\text{pre-treatment score} + 0.1) * 100$.	
End point type	Primary
End point timeframe: From baseline biopsy to surgery (2-weeks approx)	

End point values	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control	Part 2 - Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	37	19	30
Units: Patients				
Response	7	2	7	11
Non-response	31	35	12	19

End point values	Part 2 - Combination	Part 2 - Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	28		
Units: Patients				
Response	8	10		
Non-response	33	18		

Statistical analyses

Statistical analysis title	Lapatinib vs Control (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Control
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Fisher exact

Statistical analysis title	Trastuzumab vs Control (all)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Control v Part 2 - Trastuzumab v Part 2 - Control
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Fisher exact

Statistical analysis title	Combination vs Control (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Control
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Fisher exact

Statistical analysis title	Combination vs Trastuzumab (Part 2)
Comparison groups	Part 2 - Trastuzumab v Part 2 - Combination
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Fisher exact

Statistical analysis title	Trastuzumab vs Lapatinib (Part 1)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Lapatinib
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Fisher exact

Primary: Change in proliferation measured by Ki67

End point title	Change in proliferation measured by Ki67
End point description: Fall in proliferation between diagnosis and surgery: Change in proliferation measured by Ki67 immunohistochemical assessment (%) at diagnosis and at surgery. Percentage change will be defined as ((surgery score+0.1) – (pre-treatment score+0.1)/pre-treatment score+0.1)*100.	
End point type	Primary
End point timeframe: From baseline biopsy to surgery (2-weeks approx)	

End point values	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control	Part 2 - Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	44	22	31
Units: %				
median (inter-quartile range (Q1-Q3))	-14 (-51 to 6)	-43 (-68 to -21)	2 (-9 to 15)	-26 (-46 to -6)

End point values	Part 2 - Combination	Part 2 - Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	28		
Units: %				
median (inter-quartile range (Q1-Q3))	-49 (-78 to -25)	-2 (-15 to 7)		

Statistical analyses

Statistical analysis title	Lapatinib vs Control (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Control

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Trastuzumab vs Control (all)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Control v Part 2 - Trastuzumab v Part 2 - Control
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Combination vs Control (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Control
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Combination vs Trastuzumab (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Trastuzumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Trastuzumab vs Lapatinib (Part 1)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Lapatinib
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034
Method	Wilcoxon (Mann-Whitney)

Primary: Change in apoptosis

End point title	Change in apoptosis
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End point description:

Change in the tumour morphological apoptosis and activated caspase 3 measured at diagnosis and at surgery. Percentage change will be defined as ((surgery score+0.1) – (pre-treatment score+0.1))/pre-treatment score+0.1)*100.

End point type	Primary
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End point timeframe:

From baseline biopsy to surgery (2-weeks approx)

End point values	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control	Part 2 - Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	37	19	30
Units: %				
median (inter-quartile range (Q1-Q3))	-5 (-18 to 21)	-25 (-42 to 1)	24 (-10 to 57)	4 (-32 to 48)

End point values	Part 2 - Combination	Part 2 - Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	28		
Units: %				
median (inter-quartile range (Q1-Q3))	-34 (-56 to 10)	-2 (-15 to 63)		

Statistical analyses

Statistical analysis title	Lapatinib vs Control (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Control
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Trastuzumab vs Control (all)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Control v Part 2 - Trastuzumab v Part 2 - Control

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Combination vs Control (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Control
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Combination vs Trastuzumab (Part 2)
Comparison groups	Part 2 - Trastuzumab v Part 2 - Combination
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Trastuzumab vs Lapatinib (Part 1)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Lapatinib
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)

Secondary: Relapse Free Survival

End point title	Relapse Free Survival
End point description: Time from randomization to local, regional, distant tumor recurrence, or death from any cause, with second primary cancers censored.	
End point type	Secondary
End point timeframe: 5-year Relapse free survival	

End point values	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control	Part 2 - Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	51	22	32
Units: %				
number (confidence interval 95%)	88 (76 to 94)	90 (77 to 96)	95 (77 to 99)	87 (69 to 95)

End point values	Part 2 - Combination	Part 2 - Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	29		
Units: %				
number (confidence interval 95%)	92 (83 to 97)	90 (71 to 97)		

Statistical analyses

Statistical analysis title	Lapatinib vs Control (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Control
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Logrank

Statistical analysis title	Trastuzumab vs Control (all)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Control v Part 2 - Trastuzumab v Part 2 - Control
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Logrank

Statistical analysis title	Combination vs Control (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Control

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Logrank

Statistical analysis title	Combination vs Trastuzumab (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Trastuzumab
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	Logrank

Statistical analysis title	Trastuzumab vs Lapatinib (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Trastuzumab
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Logrank

Secondary: Time to local recurrence

End point title	Time to local recurrence ^[2]
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End point description:

This is defined as time from randomisation to first confirmed local recurrence. Patients who were alive and disease free at the end of follow-up were censored at the date last seen alive; patients who died were censored at date of death. Patients who have had a prior distant recurrence or second primary cancer were censored at the confirmation of this relapse.

End point type	Secondary
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End point timeframe:

5-year relapse-free rate

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No local recurrences occurred in Part 1.

End point values	Part 2 - Trastuzumab	Part 2 - Combination	Part 2 - Control	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	66	29	
Units: %				
number (confidence interval 95%)	97 (79 to 99)	97 (88 to 99)	100 (100 to 100)	

Statistical analyses

Statistical analysis title	Combination vs Control (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Control
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Logrank

Statistical analysis title	Combination vs Trastuzumab (Part 2)
Comparison groups	Part 2 - Trastuzumab v Part 2 - Combination
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Logrank

Secondary: Time to distant recurrence

End point title	Time to distant recurrence
End point description:	
End point type	Secondary
End point timeframe:	
5-year recurrence-free rate	

End point values	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control	Part 2 - Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	51	22	32
Units: %				
number (confidence interval 95%)	88 (76 to 94)	90 (77 to 96)	95 (72 to 99)	87 (69 to 95)

End point values	Part 2 - Combination	Part 2 - Control		
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Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	29		
Units: %				
number (confidence interval 95%)	94 (85 to 98)	90 (71 to 97)		

Statistical analyses

Statistical analysis title	Lapatinib vs Control (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Control
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Logrank

Statistical analysis title	Combination vs Control (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Control
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Logrank

Statistical analysis title	Trastuzumab vs Control (all)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Control v Part 2 - Trastuzumab v Part 2 - Control
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Logrank

Statistical analysis title	Combination vs Trastuzumab (Part 2)
Comparison groups	Part 2 - Trastuzumab v Part 2 - Combination
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Logrank

Statistical analysis title	Trastuzumab vs Lapatinib (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Trastuzumab
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Logrank

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Secondary
End point timeframe:	
5 year overall survival	

End point values	Part 1 - Trastuzumab	Part 1 - Lapatinib	Part 1 - Control	Part 2 - Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	51	22	32
Units: %				
number (confidence interval 95%)	91 (80 to 96)	98 (87 to 99)	100 (100 to 100)	93 (76 to 98)

End point values	Part 2 - Combination	Part 2 - Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	29		
Units: %				
number (confidence interval 95%)	98 (90 to 99)	90 (71 to 97)		

Statistical analyses

Statistical analysis title	Lapatinib vs Control (Part 1)
Comparison groups	Part 1 - Lapatinib v Part 1 - Control

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Logrank

Statistical analysis title	Trastuzumab vs Lapatinib (Part 1)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Lapatinib
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	Logrank

Statistical analysis title	Combination vs Control (Part 2)
Comparison groups	Part 2 - Combination v Part 2 - Control
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	Logrank

Statistical analysis title	Combination vs Trastuzumab (Part 2)
Comparison groups	Part 2 - Trastuzumab v Part 2 - Combination
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Logrank

Statistical analysis title	Trastuzumab vs Control (all)
Comparison groups	Part 1 - Trastuzumab v Part 1 - Control v Part 2 - Trastuzumab v Part 2 - Control
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After randomisation and within 30 days of the last administration of perioperative (28 days) trastuzumab or lapatinib.

Cardiac toxicity up to 5 years post randomisation

Adverse event reporting additional description:

Any untoward medical occurrence or effect that occurs after randomisation and within 30 days of the last administration of perioperative (28 days) trastuzumab or lapatinib.

An additional cardiac assessment after treatment but before adjuvant chemotherapy was introduced as of April 2014, affecting 90/127 part 2 patients.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Part 1&2 - Trastuzumab
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Reporting group description:

Peri-operative trastuzumab, starting 11 days (+2 or -1day) prior to surgery on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery

Reporting group title	Part 1 - Lapatinib
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Reporting group description:

Lapatinib for 28 days commencing 11 days 11 days (+2 or -1day) prior to surgery

Reporting group title	Part 2 - Combination
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Reporting group description:

Peri-operative treatment, starting 11 days (+2 or -1day) prior to surgery:

- Trastuzumab, on Day 1 and 8, and between Day 15 and Day 19 i.e. after surgery

- Lapatinib for 28 days commencing 11 days 11 days (+2 or -1day) prior to surgery

Serious adverse events	Part 1&2 - Trastuzumab	Part 1 - Lapatinib	Part 2 - Combination
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 87 (6.90%)	5 / 49 (10.20%)	5 / 65 (7.69%)
number of deaths (all causes)	10	4	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 87 (0.00%)	2 / 49 (4.08%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haematoma			

subjects affected / exposed	0 / 87 (0.00%)	1 / 49 (2.04%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 87 (0.00%)	0 / 49 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	1 / 87 (1.15%)	0 / 49 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 87 (1.15%)	0 / 49 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 87 (1.15%)	0 / 49 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 87 (1.15%)	0 / 49 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 49 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			

subjects affected / exposed	0 / 87 (0.00%)	1 / 49 (2.04%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 87 (1.15%)	2 / 49 (4.08%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 87 (1.15%)	0 / 49 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 87 (0.00%)	1 / 49 (2.04%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Breast cellulitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 49 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1&2 - Trastuzumab	Part 1 - Lapatinib	Part 2 - Combination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 87 (5.75%)	41 / 49 (83.67%)	51 / 65 (78.46%)
Cardiac disorders			
Ejection fraction abnormal	Additional description: An additional cardiac assessment after treatment but before adjuvant chemotherapy was introduced as of April 2014, affecting 90/127 part 2 patients. The assessment was done on 70/90 part 2 patients - but number exposed can't be changed below.		
subjects affected / exposed	1 / 87 (1.15%)	0 / 49 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea	Additional description: Diaphorrea was recorded retrospectively, and only whether patient had experienced episode or not (not number of episodes)		

subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	25 / 49 (51.02%) 25	37 / 65 (56.92%) 37
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash was assessed retrospectively, and only if patients had experienced an episode - number of episodes not collected.		
subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	38 / 49 (77.55%) 38	33 / 65 (50.77%) 33

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2010	Changes to Patient Information Sheet and consent forms
08 September 2011	Addition of Northern Ireland as a location in the UK plus addition of sites and changes to Patient Information Sheet, Consent form and protocol.
01 October 2012	Updated protocol, updated GP letter, changes to labelling of Investigational Medicinal Product
10 April 2013	- Protocol -updated - IMP label Amendment (Lapatinib 1000mg) - PIS/CFs (Pathway A, B, and Non Biological) - Patient Summaries (Pathway A, B, and Non Biological) - GP letter updated - Patient Card updated - Change of Principal Investigators at two sites
18 December 2013	Additional assessment of cardiac function: The EPHOS-B IDMC stated that, although there did not appear to be a safety concern around symptomatic left ventricular dysfunction, a more detailed study of cardiac function was necessary to reassure clinicians that there were no adverse cardiac sequelae caused by the administration of anti-her2 therapies in the peri-operative period. To this end the inclusion of an assessment of cardiac function in the post-operative period prior to the initiation of systemic adjuvant chemotherapy was then mandatory. Updates to Patient Information Sheet and consent. Change of PI at one centre
26 April 2018	A change in the legal name of one of the three EPHOS-B Co-Sponsors. On 1 October 2017, University Hospital of South Manchester (UHSM) and Central Manchester University Hospitals NHS Foundation Trust joined together as a single organisation, called Manchester University NHS Foundation Trust (MFT). The effective date of transfer of responsibilities from UHSM to MFT was therefore 1 October 2017. The EPHOS-B Co-Sponsors are The Institute of Cancer Research, The University of Manchester and Manchester University NHS Foundation Trust.
04 September 2019	Updates to protocol- n 2015 Novartis acquired the GSK oncology portfolio and therefore references to GSK have been updated in the protocol where appropriate, plus administrative changes and removal for the requirement for annual cardiac assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35165099>