Clinical trial results:
Avastin Randomised Trial with neo-adjuvant chemotherapy for patients with early HER2- negative breast cancer

Summary

EudraCT number	2008-002322-11
Trial protocol	GB
Global end of trial date	19 June 2014

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	31 July 2015
Summary attachment (see zip file)	Artemis Article (ARTemis_LancetOncologyArticle_May2015.pdf) Artemis SupplementaryAppendix (ARTemis_LancetOncology_SupplementaryAppendix_May2015.pdf)

Trial information

Trial identification

Sponsor protocol code	ARTemis

Additional study identifiers

ISRCTN number	ISRCTN68502941
ClinicalTrials.gov id (NCT number)	NCT01093235
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
Sponsor organisation address	R&D, Box 277, Addenbrooke's Hospital, Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Louise Grybowicz , Cambridge University Hospitals NHS Foundation Trust, +44 1223 348447, louise.grybowicz@addenbrookes.nhs.uk
Scientific contact	Dr. Helena Earl, University of Cambridge , hme22@cam.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	16 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2014
Global end of trial reached?	Yes
Global end of trial date	19 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A phase III, randomised trial to determine whether the addition to neo-adjuvant chemotherapy (3 cycles of docetaxel followed by 3 cycles of 5-fluorouracil, epirubicin and cyclophosphamide) of 4 cycles of an anti-angiogenic agent bevacizumab given concurrently with the chemotherapy is more effective than standard chemotherapy alone in terms of short-term and long-term outcome in patients presenting with high risk HER2-negative early breast cancer.

Protection of trial subjects:

Protocol design: Prevention of AEs included cardiac monitoring (LVEF and BP) mandated before, during and after treatment; G-CSF strongly recommended for use alongside treatment; schedule of chemotherapy reversed to be less cardiotoxic and more efficacious; mandatory treatment washout period before surgery; early interim safety analysis of toxicities on first 200 patients; various exclusion criteria, screening, and on-treatment investigations conducted to ascertain and maintain knowledge of patients' fitness to receive the treatment; on-study toxicity management guidelines; and continuous monitoring and dissemination of the safety data for the treatments used throughout the trial, and of the patients themselves.

Background therapy:

5-Fluorouracil 500mg/m2, Epirubicin 100mg/m2 and Cyclophosphamide 500mg/m2: every 3 weeks for 3 cycles.

Evidence for comparator: -

Actual start date of recruitment	07 May 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 800
Worldwide total number of subjects	800
EEA total number of subjects	800

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)	758
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were approached, consented, and recruited at hospital oncology clinics for recently-diagnosed, HER-2 negative, early (non-metastatic) breast cancer. Recruitment period was from May 2009 to Jan 2013.

Pre-assignment

Screening details:

HER2, ER, FBC, biochem, BP, Pregnancy, Urine, Coagulation, LVEF, Staging inflammatory/LN+
Exclusions: Cardiac-related or Thromboembolic disease, Inflammatory GI disease, Bleeding diathesis, Nephritic/nephrotic syndrome, Infection, Major surgery/trauma, Non-healing wound/fracture, Anticoagulants, LHRH-agonists, Other chemo/bio agent or malignancy.

Pre-assignment period milestones

Number of subjects started	800
Number of subjects completed	800

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm B

Arm description:

Research

Arm type	Experimental
Investigational medicinal product name	Bevacizumab (Avastin)
Investigational medicinal product code	Bev
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15mg/kg; IV infusion every 3 weeks, for 4 cycles.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	D
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100mg/m2, every 3 weeks for 3 cycles.

Arm title	Arm A

Arm description:

Standard treatment

Arm type	Active comparator

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	D
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100mg/m2, every 3 weeks for 3 cycles.

Number of subjects in period 1	Arm B	Arm A
Started	399	401
Completed	388	393
Not completed	11	8
Physician decision	1	1
Consent withdrawn by subject	7	7
'disease progression '	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm B
Reporting group description: Research	

Reporting group title	Arm A
Reporting group description: Standard treatment	

Reporting group values	Arm B	Arm A	Total
Number of subjects	399	401	800
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)	377	381	758
From 65-84 years	22	20	42
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	399	401	800
Male	0	0	0
ER status Units: Subjects			
ER negative	122	126	248
ER weakly positive	37	38	75
ER strongly positive	240	237	477
Tumour Size Units: Subjects			
<=50mm	317	318	635
>50mm	82	83	165
Clinical involvement of axillary nodes Units: Subjects			
No	190	193	383
Yes	209	208	417

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

Subject analysis set description:
All randomised patients.

Reporting group values	ITT		
Number of subjects	800		
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)	758		
From 65-84 years	42		
85 years and over	0		
Gender categorical Units: Subjects			
Female	800		
Male	0		
ER status Units: Subjects			
ER negative	248		
ER weakly positive	75		
ER strongly positive	477		
Tumour Size Units: Subjects			
<=50mm	635		
>50mm	165		
Clinical involvement of axillary nodes Units: Subjects			
No	383		
Yes	417		

End points

End points reporting groups

Reporting group title	Arm B
Reporting group description: Research	

Reporting group title	Arm A
Reporting group description: Standard treatment	

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomised patients.	

Primary: Complete pathological response (pathCR) rates (tumour and lymph nodes) after neo-adjuvant chemotherapy.

End point title	Complete pathological response (pathCR) rates (tumour and lymph nodes) after neo-adjuvant chemotherapy.
End point description: No residual invasive carcinoma within the breast (DCIS permitted) AND no evidence of metastatic disease within the lymph nodes {Pinder, 2007 #86}	
End point type	Primary
End point timeframe: Period of assessment: 02July2013 - 11Mar2014	

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	393		
Units: pathological complete response (pCR)				
Yes	87	66		
No	301	327		

Statistical analyses

Statistical analysis title	Complete pathological response (pathCR) rates.
Statistical analysis description: No residual invasive carcinoma within the breast (DCIS permitted) AND no evidence of metastatic disease within the lymph nodes {Pinder, 2007 #86}	
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	781
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.26

Notes:

[1] - "Multivariate logistic regression provided p values for the treatment effect after adjustment for stratification factors."

Secondary: pCR and Minimal Residual Disease (MRD)

End point title	pCR and Minimal Residual Disease (MRD)

End point description:

Complete pathological response (pathCR) and Minimal Residual Disease (MRD) rates (tumour and lymph nodes) after neo-adjuvant chemotherapy.

End point type	Secondary

End point timeframe:

Period of assessment: 02July2013 - 11Mar2014

End point values	Arm B	Arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	394		
Units: subjects				
Yes	138	114		
No	250	280		

Statistical analyses

Statistical analysis title	pCR and Minimal Residual Disease (MRD)

Statistical analysis description:

Complete pathological response (pathCR) and Minimal Residual Disease (MRD) rates (tumour and lymph nodes) after neo-adjuvant chemotherapy.

Comparison groups	Arm B v Arm A

Number of subjects included in analysis	782
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.03 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.98

Notes:

[2] - "Multivariate logistic regression provided p values for the treatment effect after adjustment for stratification factors."

Statistical analysis title	pCR in breast only

Statistical analysis description:

pCR in all breast tumours

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	782
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.24

Notes:

[3] - "Multivariate logistic regression provided p values for the treatment effect after adjustment for stratification factors."

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation of the first trial patient, to 6 weeks after the final infusion of the final patient (or longer if considered related to treatment or protocol).

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	All patients

Reporting group description:

All patients randomised into the trial

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	362 / 800 (45.25%)		
number of deaths (all causes)	90		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thrombosis / Thrombus / Embolism [10043607]			
subjects affected / exposed	9 / 800 (1.13%)		
occurrences causally related to treatment / all	3 / 9		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutrophils [10029366]	Additional description: Low neutrophils		
subjects affected / exposed	55 / 800 (6.88%)		
occurrences causally related to treatment / all	40 / 64		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever [10016558]	Additional description: In the absence of neutropenia		
subjects affected / exposed	36 / 800 (4.50%)		
occurrences causally related to treatment / all	27 / 39		
deaths causally related to treatment / all	0 / 0		
Pain: Other [90004082]			

subjects affected / exposed	21 / 800 (2.63%)		
occurrences causally related to treatment / all	15 / 21		
deaths causally related to treatment / all	0 / 0		
Other	Additional description: All other events <10% of patients reported		
subjects affected / exposed	92 / 800 (11.50%)		
occurrences causally related to treatment / all	64 / 99		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction/hypersensitivity (including drug fever) [10020751]			
subjects affected / exposed	36 / 800 (4.50%)		
occurrences causally related to treatment / all	38 / 38		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea [10012727]			
subjects affected / exposed	18 / 800 (2.25%)		
occurrences causally related to treatment / all	13 / 18		
deaths causally related to treatment / all	0 / 0		
Vomiting [10047700]			
subjects affected / exposed	12 / 800 (1.50%)		
occurrences causally related to treatment / all	5 / 12		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile neutropenia [10016288]			
subjects affected / exposed	171 / 800 (21.38%)		
occurrences causally related to treatment / all	152 / 185		
deaths causally related to treatment / all	0 / 0		
Infection: Other [10021789]	Additional description: All types		
subjects affected / exposed	83 / 800 (10.38%)		
occurrences causally related to treatment / all	66 / 88		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	800 / 800 (100.00%)		
Cardiac disorders			
Hypertension (10020772)			
subjects affected / exposed	89 / 800 (11.13%)		
occurrences (all)	174		
Nervous system disorders			
Peripheral neuropathy (10034620)	Additional description: Any grade		
subjects affected / exposed	403 / 800 (50.38%)		
occurrences (all)	977		
General disorders and administration site conditions			
Fatigue (10016256)			
subjects affected / exposed	720 / 800 (90.00%)		
occurrences (all)	2978		
Other	Additional description: All other events reported		
subjects affected / exposed	731 / 800 (91.38%)		
occurrences (all)	7051		
Blood and lymphatic system disorders			
Neutropenia (10029366)	Additional description: Any grade		
subjects affected / exposed	353 / 800 (44.13%)		
occurrences (all)	527		
Gastrointestinal disorders			
Constipation (10010774)	Additional description: Any grade		
subjects affected / exposed	478 / 800 (59.75%)		
occurrences (all)	1150		
Diarrhoea (10012727)	Additional description: Any grade		
subjects affected / exposed	430 / 800 (53.75%)		
occurrences (all)	852		
Nausea (10028813)			
subjects affected / exposed	613 / 800 (76.63%)		
occurrences (all)	1634		
Vomiting (10047700)			
subjects affected / exposed	283 / 800 (35.38%)		
occurrences (all)	489		
Skin and subcutaneous tissue disorders			

Alopecia (10001760)	Additional description: Any grade		
subjects affected / exposed	719 / 800 (89.88%)		
occurrences (all)	3495		
Infections and infestations			
Infection (10021789)	Additional description: Any grade		
subjects affected / exposed	361 / 800 (45.13%)		
occurrences (all)	596		
Metabolism and nutrition disorders			
Proteinuria (10037020)	Additional description: Any grade		
subjects affected / exposed	65 / 800 (8.13%)		
occurrences (all)	100		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2009	Administrative changes & clarifications to Protocol & Patient Information Sheets; addition of screening tests and time limits to pre-randomisation tests; long-term follow-up increased to 10 years.
22 June 2010	New reference safety information (Summary of Product Characteristics) for IMP docetaxel
18 October 2010	Change of distributor of IMP Bevacizumab - outsourced by the manufacturer.
27 September 2011	Administrative changes & clarifications to Protocol & Patient Information Sheets; addition of eligibility criteria; interim saftey analysis complete, requirement to report specific AEs lifted.
29 October 2013	Addition of a translational sample collection sub-study; clarification of primary endpoint; clarification of definition of end of trial.

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/25975632