Clinical trial results:
A phase II/III, randomised, two-arm comparison of maintenance lapatinib versus placebo after firrst-line chemotherapy in patients with HER1 and/or HER2 over expressing locally advanced or metastatic bladder cancer.

Summary

EudraCT number	2007-001826-28
Trial protocol	GB
Global end of trial date	07 September 2015

Results information

Result version number	v1 (current)
This version publication date	16 August 2017
First version publication date	16 August 2017
Summary attachment (see zip file)	JCO 2016 Powles et al (Powles et al. LaMB_J Clin Oncol_2016.pdf)

Trial information

Trial identification

Sponsor protocol code	BL-2007-02

Additional study identifiers

ISRCTN number	ISRCTN35418671
ClinicalTrials.gov id (NCT number)	NCT00949455
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University London
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Charlotte Ackerman, Centre for Experimental Cancer Medicine, +44 2078828497, bci-lamb@qmul.ac.uk
Scientific contact	Thomas Powles, Centre for Experimental Cancer Medicine, +44 2078828497, bci-lamb@qmul.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	07 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to compare progression-free survival (PFS) in patients with HER1 and/or HER2 over expressing stage IV bladder cancer who have been randomised to maintenance therapy with lapatinib or placebo following first-line chemotherapy

Protection of trial subjects:

Patients were closely monitored as part of the clinical trial and were seen monthly. ECHOs were carried out in case of any cardiac issues from the lapatinib. The standard of care for these patients is surveillance, and therefore no patients were deviating from this by having placebo.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 February 2009
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: 232
Worldwide total number of subjects	232
EEA total number of subjects	232

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)	59
From 65 to 84 years	169
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

From 17/2/2009, 455 patients were screened for eligibility for the LaMB trial. 236 patients were subsequently randomised to treatment. Patients were recruited from multiple centres within the UK only.

Pre-assignment

Screening details:

Patients with histologically confirmed metastatic or locally advanced stage IV transitional cell carcinoma of the urothelium and with an objective response or stable disease upon completion of first-line chemotherapy, were tested for HER1/2 status. Patients with positive status were randomised between lapatinib and placebo maintenance treatment.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Lapatinib

Arm description:

IMP

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 was given continuously at 1500mg once daily (6 x 250mg tablets). In the placebo group 6 visually identical tablets were given instead.

Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

6 visually identical tablets to lapatinib

Number of subjects in period 1	Lapatinib	Placebo
Started	116	116
Completed	116	116

Baseline characteristics

Reporting groups	
Reporting group title	Lapatinib
Reporting group description: IMP	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Lapatinib	Placebo	Total
Number of subjects	116	116	232
Age categorical Units: Subjects			
Adults (18-64 years)	29	30	59
From 65-84 years	81	79	160
85 years and over	2	2	4
Not recorded	4	5	9
Age continuous Units: years			
median	70.7	71.1	
inter-quartile range (Q1-Q3)	63.9 to 77.2	63.8 to 76.3	-
Gender categorical Units: Subjects			
Female	28	32	60
Male	88	84	172
ECOG performance status			
ECOG performance status			
Units: Subjects			
Fully active	53	52	105
Ambulatory, capable of light work	52	51	103
Ambulatory but not capable of work	11	13	24
Response to previous chemotherapy Units: Subjects			
CR or PR	80	78	158
SD	36	38	74
PD	0	0	0
Tumour grade Units: Subjects			
Grade 1 or 2	4	4	8
Grade 3 or 4	98	98	196
not recorded	14	14	28
Visceral metastasis Units: Subjects			
Yes	60	47	107
No	52	62	114
not recorded	4	7	11
HER status Units: Subjects			

HER1 positive	53	49	102
HER2 positive	21	21	42
HER1 and HER2 positive	42	46	88
HER negative	0	0	0
Previous cisplatin base chemotherapy Units: Subjects			
Yes	71	73	144
No	40	39	79
Not recorded	5	4	9
Haemoglobin Units: Subjects			
Normal	31	26	57
Low	78	90	168
not recorded	7	0	7
Albumin Units: Subjects			
Normal	108	111	219
Low	1	3	4
not recorded	7	2	9
Creatinine Units: Subjects			
Normal	49	36	85
High	60	78	138
not recorded	7	2	9

Subject analysis sets

Subject analysis set title	Trial patient analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients who meet inclusion/exclusion criteria and were randomised to receive treatment

Reporting group values	Trial patient analysis		
Number of subjects	232		
Age categorical Units: Subjects			
Adults (18-64 years)	59		
From 65-84 years	160		
85 years and over	4		
Not recorded	9		
Age continuous Units: years			
median	70.7		
inter-quartile range (Q1-Q3)	64.2 to 77.1		
Gender categorical Units: Subjects			
Female	60		
Male	172		

ECOG performance status			
ECOG performance status			
Units: Subjects			
Fully active	105		
Ambulatory, capable of light work	103		
Ambulatory but not capable of work	24		
Response to previous chemotherapy Units: Subjects			
CR or PR	158		
SD	74		
PD	0		
Tumour grade Units: Subjects			
Grade 1 or 2	8		
Grade 3 or 4	196		
not recorded	28		
Visceral metastasis Units: Subjects			
Yes	107		
No	114		
not recorded	11		
HER status Units: Subjects			
HER1 positive	102		
HER2 positive	42		
HER1 and HER2 positive	88		
HER negative	0		
Previous cisplatin base chemotherapy Units: Subjects			
Yes	144		
No	79		
Not recorded	9		
Haemoglobin Units: Subjects			
Normal	57		
Low	168		
not recorded	7		
Albumin Units: Subjects			
Normal	219		
Low	4		
not recorded	9		
Creatinine Units: Subjects			
Normal	85		
High	138		
not recorded	9		

End points

End points reporting groups

Reporting group title	Lapatinib
Reporting group description: IMP	
Reporting group title	Placebo
Reporting group description: Placebo	
Subject analysis set title	Trial patient analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients who meet inclusion/exclusion criteria and were randomised to receive treatment	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe: Date of randomisation until disease progression or death from any cause	

End point values	Lapatinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	116		
Units: months				
median (confidence interval 95%)	4.5 (2.8 to 5.4)	5.1 (3 to 5.8)		

Statistical analyses

Statistical analysis title	Progression-free survival
Comparison groups	Lapatinib v Placebo
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.43

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Date of randomisation until death from any cause

End point values	Lapatinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	116		
Units: months				
median (confidence interval 95%)	12.6 (9 to 16.2)	12 (10.5 to 14.9)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Lapatinib v Placebo
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.31

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire trial

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTC
Dictionary version	4.03

Reporting groups

Reporting group title	Lapatinib
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Lapatinib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 116 (70.69%)	82 / 116 (70.69%)	
number of deaths (all causes)	42	42	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	4 / 116 (3.45%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	1 / 116 (0.86%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	10 / 116 (8.62%)	6 / 116 (5.17%)	
occurrences causally related to treatment / all	2 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			

Pulmonary/Upper Respiratory			
subjects affected / exposed	1 / 116 (0.86%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	3 / 116 (2.59%)	6 / 116 (5.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Investigations			
subjects affected / exposed	2 / 116 (1.72%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	0 / 116 (0.00%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	2 / 116 (1.72%)	3 / 116 (2.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous System Disorder			
subjects affected / exposed	2 / 116 (1.72%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	0 / 116 (0.00%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastrointestinal disorders			
subjects affected / exposed	7 / 116 (6.03%)	7 / 116 (6.03%)	
occurrences causally related to treatment / all	6 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	1 / 116 (0.86%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	0 / 116 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	10 / 116 (8.62%)	11 / 116 (9.48%)	
occurrences causally related to treatment / all	1 / 14	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	0 / 116 (0.00%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and Infestations			
subjects affected / exposed	8 / 116 (6.90%)	5 / 116 (4.31%)	
occurrences causally related to treatment / all	1 / 9	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	0 / 116 (0.00%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lapatinib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 116 (83.62%)	99 / 116 (85.34%)	
Cardiac disorders			
Hypertension			
subjects affected / exposed	4 / 116 (3.45%)	7 / 116 (6.03%)	
occurrences (all)	4	7	
Nervous system disorders			
Neuropathy			
subjects affected / exposed	7 / 116 (6.03%)	14 / 116 (12.07%)	
occurrences (all)	7	14	
Neurotoxicity			
subjects affected / exposed	7 / 116 (6.03%)	1 / 116 (0.86%)	
occurrences (all)	7	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 116 (1.72%)	10 / 116 (8.62%)	
occurrences (all)	2	10	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 116 (32.76%)	42 / 116 (36.21%)	
occurrences (all)	38	42	
Oedema			
subjects affected / exposed	5 / 116 (4.31%)	8 / 116 (6.90%)	
occurrences (all)	5	8	
Pain			
subjects affected / exposed	47 / 116 (40.52%)	47 / 116 (40.52%)	
occurrences (all)	47	47	
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	16 / 116 (13.79%)	18 / 116 (15.52%)	
occurrences (all)	16	18	
Diarrhoea			
subjects affected / exposed	58 / 116 (50.00%)	23 / 116 (19.83%)	
occurrences (all)	65	23	
Nausea			
subjects affected / exposed	23 / 116 (19.83%)	20 / 116 (17.24%)	
occurrences (all)	23	20	
Vomiting			
subjects affected / exposed	18 / 116 (15.52%)	16 / 116 (13.79%)	
occurrences (all)	18	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 116 (6.90%)	10 / 116 (8.62%)	
occurrences (all)	8	10	
Respiratory			
subjects affected / exposed	3 / 116 (2.59%)	7 / 116 (6.03%)	
occurrences (all)	3	7	
Shortness of breath			
subjects affected / exposed	12 / 116 (10.34%)	10 / 116 (8.62%)	
occurrences (all)	12	10	
Hepatobiliary disorders			
Creatinine			
subjects affected / exposed	4 / 116 (3.45%)	7 / 116 (6.03%)	
occurrences (all)	4	7	
Skin and subcutaneous tissue disorders			
Cutaneous			
subjects affected / exposed	5 / 116 (4.31%)	1 / 116 (0.86%)	
occurrences (all)	5	1	
Dry skin			
subjects affected / exposed	6 / 116 (5.17%)	2 / 116 (1.72%)	
occurrences (all)	6	2	
Itch			
subjects affected / exposed	12 / 116 (10.34%)	10 / 116 (8.62%)	
occurrences (all)	12	12	
Rash			

subjects affected / exposed	45 / 116 (38.79%)	21 / 116 (18.10%)	
occurrences (all)	45	21	
Renal and urinary disorders			
Bladder symptoms			
subjects affected / exposed	5 / 116 (4.31%)	6 / 116 (5.17%)	
occurrences (all)	6	6	
Haematuria			
subjects affected / exposed	11 / 116 (9.48%)	6 / 116 (5.17%)	
occurrences (all)	11	6	
Renal Impairment			
subjects affected / exposed	6 / 116 (5.17%)	7 / 116 (6.03%)	
occurrences (all)	6	7	
Infections and infestations			
Infection			
subjects affected / exposed	31 / 116 (26.72%)	18 / 116 (15.52%)	
occurrences (all)	31	18	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	12 / 116 (10.34%)	7 / 116 (6.03%)	
occurrences (all)	12	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2008	Addition of an interim analysis to the protocol Prohinbited drugs list added to PIS Scan schedule changed to every 12 weeks rather than 10 weeks Correction to IMP storage conditions in protocol.
11 February 2009	Study amended from Phase III to Phase II/III. Administrative corrections throughout protocol. Two stratification factors removed from the randomisation (prior ciplatin chemotherapy, hospital site) Inclusion of patients with HER2+ intensity on IHC Haemaglobin levels (>8.0 g/dL) added to inclusion criteria Clarifications to assessment schedule Instructions to sites regarding IMP management at end of the study added to protocol Dose management guidance added to protocol in the event of liver chemistry, LVEF and hepatobiliary abnormalities
02 July 2009	Patients with bladder cancer in the urothelial tract eligible for entry. Following updated safety information from IMP manufacturer - herbal supplements are prohibited from use and diarrhoea supportive care guidance provided.
25 August 2009	Amendment to allow metastatic bladder cancer patients with bone metastases (alkaline phosphatase levels removed from the inclusion criteria). Administrative clarifications to assessment schedule
24 May 2010	Amendment to protocol to allow for capture of follow-up data for all patients screened that are HER negative, but did not proceed to study treatment. Addition of testing for HER3 and 4 status Administrative clarifications to protocol
18 October 2010	Update to exclusion criteria - remove previous HER1/2 therapy from the exclusion criteria Time allowed between randomisation and treatment commencement increased to 10 weeks
13 January 2011	Addition of sites and change of Principal Investigator only
19 May 2011	Amendment to protocol to allow for capture of follow-up data for all patients screened that are HER positive, but did not proceed to study treatment.
23 June 2011	Addition of sites and change of Principal Investigator only
30 November 2011	Changes to Principal Investigators only
17 April 2012	Addition of new sites only
01 August 2012	Change of Principal Investigator only
22 October 2012	Change of Principal Investigator only

30 July 2013	Increase to sample size Change to Principal Investigators
27 January 2015	Clarification of end of trial procedures in protocol

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/28034079