Clinical trial results:
Randomised phase II window study of short-term preoperative treatment with the PI3K inhibitor GDC-0941 plus Anastrozole versus Anastrozole alone in patients with ER-positive primary breast cancer

Summary

EudraCT number	2011-003530-13
Trial protocol	GB
Global end of trial date	09 November 2015

Results information

Result version number	v1 (current)
This version publication date	03 January 2020
First version publication date	03 January 2020
Summary attachment (see zip file)	Clinical Study Report 2011-003530-13 (Opportune CRS_v1.0_19Dec2018.pdf)

Trial information

Trial identification

Sponsor protocol code	18072011

Additional study identifiers

ISRCTN number	ISRCTN26131497
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Brighton & Sussex University Hospitals NHS Trust
Sponsor organisation address	Eastern Road, Brighton, United Kingdom, BN2 5BE
Public contact	Head of Research & Development, Brighton & Sussex University Hospitals NHS Trust, +44 01273696955, bsuh.sponsorship.approvals@nhs.net
Scientific contact	Head of Research & Development, Brighton & Sussex University Hospitals NHS Trust, +44 01273696955, bsuh.sponsorship.approvals@nhs.net

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	04 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In women with ER-positive breast cancer about to undergo surgery, does two week's pretreatment with a new drug (the PI3K inhibitor GDC-0941, given in combination with the estrogen-blocker anastrozole) increase the benefits of anastrozole in slowing down tumour cell growth, as measured by laboratory measurements on tumour cells?

Protection of trial subjects:

The current experience with single agent GDC-0941 in cancer patients confirms that GDC-0941 can be given safely and is associated with an acceptable toxicity profile. However, GDC-0941 remains an experimental agent and additional side effects might be described at later stages. Most studies to date included heavily pre-treated patients with advanced or metastatic cancers. The majority of adverse effects in these studies were grade 1 or 2 and were generally rapidly reversible. The incidence of moderate or severe toxicities was low, especially during the first 2 weeks of treatment. Consequently, the risks associated with 15 days of preoperative treatment with GDC-0941 as part of this trial are expected to be low. All enrolled patients were evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations consisted of medical interviews, recording of adverse events, physical examinations, ECG recordings, and laboratory measurements. Patients were evaluated for adverse events (all grades), serious adverse events, and any adverse events requiring drug interruption or discontinuation throughout the course of the study. Two committees were convened to evaluate the safety of this trial. The first committee was the Trial Management Group (TMG), which was composed of the chief investigator, principal investigators from each site, the study statistician, the study co-ordinator and the trial pharmacist. The second committee was a scientific Trial Steering Committee, composed of external advisors who advised the Sponsor and the TMG on data interpretation and appropriate modifications to the study, if appropriate.

Safety assessments consisted of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified haematology, clinical chemistry, coagulation variables; measurement of protocol-specified vital signs; and other protocol

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 167
Worldwide total number of subjects	167
EEA total number of subjects	167

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)	85
From 65 to 84 years	80
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Between January 2012 and September 2015 180 patients were screened across 11 sites in the UK. 167 were randomized.

Pre-assignment

Screening details:

Confined to postmenopausal women with newly diagnosed, ER-positive, HER2- negative, invasive primary breast cancer. 13 screening failures based on protocol defined inclusion and exclusion criteria. 2 further patients excluded post randomization but prior to treatment due to consequent violations of key eligibility criteria and 2 withdrew consent.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Anastrazole only

Arm description:

Comparitor

Arm type	Active comparator
Investigational medicinal product name	Anastrazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1mg OD

Arm title	Anastrazole + Pictilisib

Arm description:

Treatment arm

Arm type	Experimental
Investigational medicinal product name	Anastrazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1mg OD

Investigational medicinal product name	Pictilisib
Investigational medicinal product code	
Other name	GDC-0941
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

340mg OD (5 evaluable patients) reduced to 260mg OD

Number of subjects in period 1[1]	Anastrazole only	Anastrazole + Pictilisib
Started	46	90
Completed	46	90

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 2 patients withdrew consent and 29 patients were not evaluable due to protocol deviations

Period 2

Period 2 title	End of Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Anastrozole

Arm description:

Anastrozole treatment until surgery on day 15

Arm type	Active comparator
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	Arimidex
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Anastrozole 1 mg OD orally

Arm title	Anastrazole + Pictilisib

Arm description:

Anastrozole combined with PI3K inhibitor pictilisib until surgery on day 15

Arm type	Experimental
Investigational medicinal product name	GDC-0941
Investigational medicinal product code	RO5314482
Other name	Pictilisib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

GDC-0941 260 mg OD orally

Number of subjects in period 2	Anastrozole	Anastrazole + Pictilisib
Started	46	90
Completed	46	90

Baseline characteristics

Reporting groups	
Reporting group title	Anastrazole only
Reporting group description:	
Comparitor	
Reporting group title	Anastrazole + Pictilisib
Reporting group description:	
Treatment arm	

Reporting group values	Anastrazole only	Anastrazole + Pictilisib	Total
Number of subjects	46	90	136
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Median (range)			
Units: years			
median	66.9	64.1	
full range (min-max)	47.7 to 85.4	48.5 to 81.1	-
Gender categorical			
Units: Subjects			
Female	46	90	136
Male	0	0	0
Tumour status			
Units: Subjects			
Grade 1	5	14	19
Grade 2	34	62	96
Grade 3	7	14	21
PR status			
Tumor is progesterone receptor (PR) positive or negative			
Units: Subjects			
Positive	34	83	117
Negative	12	7	19
PI3KCA mutation status			
phosphoinositide 3-kinase (PI3K) pathway catalytic subunit type			
Units: Subjects			
Wildtype	27	58	85
Kinase-domain mutation	14	18	32

Helical-domain mutation	5	14	19

Ki67			
Ki67 % positive tumour cells			
Units: 0-100			
median			
full range (min-max)			-

Subject analysis sets	
Subject analysis set title	Anastrazole
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomized to anastrazole only treatment	
Subject analysis set title	Anastrazole + Pictilisib
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomized to anastrazole + pictilisib	

Reporting group values	Anastrazole	Anastrazole + Pictilisib	
Number of subjects	46	90	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Median (range)			
Units: years			
median	66.9	64.1	
full range (min-max)	47.7 to 85.4	48.5 to 81.1	
Gender categorical			
Units: Subjects			
Female	46	90	
Male	0	0	
Tumour status			
Units: Subjects			
Grade 1	5	13	
Grade 2	34	62	
Grade 3	7	14	
PR status			
Tumor is progesterone receptor (PR) positive or negative			

Units: Subjects			
Positive	33	82	
Negative	11	6	
PI3KCA mutation status			
phosphoinositide 3-kinase (PI3K) pathway catalytic subunit type			
Units: Subjects			
Wildtype	27	53	
Kinase-domain mutation	14	15	
Helical-domain mutation	5	14	
Ki67			
Ki67 % positive tumour cells			
Units: 0-100			
median	23.0	22.7	
full range (min-max)	1.9 to 84.1	0.9 to 89.9	

End points

End points reporting groups	
Reporting group title	Anastrazole only
Reporting group description: Comparitor	
Reporting group title	Anastrazole + Pictilisib
Reporting group description: Treatment arm	
Reporting group title	Anastrozole
Reporting group description: Anastrozole treatment until surgery on day 15	
Reporting group title	Anastrazole + Pictilisib
Reporting group description: Anastrozole combined with PI3K inhibitor pictilisib until surgery on day 15	
Subject analysis set title	Anastrazole
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients randomized to anastrazole only treatment	
Subject analysis set title	Anastrazole + Pictilisib
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients randomized to anastrazole + pictilisib	

Primary: Effect of study treatment on cell proliferation	
End point title	Effect of study treatment on cell proliferation[1]
End point description: Quantification of tumour Ki67 expression at day 15 as a biomarker of cell proliferation	
End point type	Primary
End point timeframe: Baseline to End of Treatment (Day 15)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see attached document and charts for results

End point values	Anastrozole	Anastrazole + Pictilisib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	90		
Units: Ki67 supression				
geometric mean (confidence interval 95%)	70.7 (61.0 to 78.0)	82.5 (78.3 to 85.8)		

Attachments (see zip file)	Opportune stats/Opportune CRS_statistical analyses_extract. Primary endpoint results/Opportune CRS_primary endpoint

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of Study Treatment on Tumour Cell Apoptosis (killing cancer cells)

End point title	Effect of Study Treatment on Tumour Cell Apoptosis (killing cancer cells)

End point description:

Quantification of caspase-3 expression as a biomarker for apoptosis

End point type	Secondary

End point timeframe:

Baseline to day 15 - end of treatment

End point values	Anastrozole	Anastrazole + Pictilisib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	56		
Units: Casp-3 expression				
geometric mean (confidence interval 95%)	0.14 (0.10 to 0.18)	0.15 (0.11 to 0.19)		

Attachments (see zip file)	Apoptosis charts/Opportune CRS_secondary endpoint apoptosis

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Link between treatment and biomarker status of patient

End point title	Link between treatment and biomarker status of patient

End point description:

Comparison of interaction between PIK3CA mutation subtypes [helical domain mutations (HD), kinase domain mutations (KD), wildtype (WT)] and mean Ki67 suppression

End point type	Other pre-specified

End point timeframe:

Baseline to day 15 - end of treatment

End point values	Anastrozole	Anastrazole + Pictilisib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	90		
Units: PIK3CA mutation status				
geometric mean (confidence interval 95%)				
PI3CA Wild Type	69.9 (45.7 to 80.2)	81.1 (75.2 to 85.6)		

helical domain mutations	59.3 (42.8 to 75.7)	84.6 (66.1 to 103.3)		
kinase domain mutations	81.8 (59.7 to 103.9)	78.6 (58.4 to 98.7)		

Attachments (see zip file)	Treatment effect vs biomarker status/Opportune

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After informed consent until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later.

Adverse event reporting additional description:

monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified haematology, clinical chemistry, coagulation variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drugs

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Anastrazole
Reporting group description: -	
Reporting group title	Anastrazole + Pictilisib

Reporting group description: -

Serious adverse events	Anastrazole	Anastrazole + Pictilisib	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 54 (3.70%)	3 / 109 (2.75%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Haematoma	Additional description: Bleeding post wide local excision and sentinel node biopsy - haematoma in left axilla.		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 54 (3.70%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia supraventricular	Additional description: Supraventricular and nodal arrhythmia, sinus bradycardia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 54 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Anaphylactic reaction	Additional description: Admitted to Accident and Emergency with oedema of the tongue and treated for anaphylaxis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 54 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Ulcer	Additional description: Ulceration - wound breakdown and necrosis around excision area		
subjects affected / exposed	0 / 54 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Anastrazole	Anastrazole + Pictilisib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 54 (48.15%)	47 / 109 (43.12%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 54 (7.41%)	4 / 109 (3.67%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 54 (12.96%)	13 / 109 (11.93%)	
occurrences (all)	7	13	
Dysgeusia			
subjects affected / exposed	1 / 54 (1.85%)	6 / 109 (5.50%)	
occurrences (all)	1	6	
Anorexia nervosa	Additional description: anorexia		
subjects affected / exposed	1 / 54 (1.85%)	7 / 109 (6.42%)	
occurrences (all)	1	7	
Nausea			
subjects affected / exposed	3 / 54 (5.56%)	27 / 109 (24.77%)	
occurrences (all)	3	27	
Hyperglycaemia			

subjects affected / exposed	0 / 54 (0.00%)	4 / 109 (3.67%)	
occurrences (all)	0	4	
Hot flush			
subjects affected / exposed	6 / 54 (11.11%)	2 / 109 (1.83%)	
occurrences (all)	6	2	
Immune system disorders			
Rash generalised			
subjects affected / exposed	0 / 54 (0.00%)	9 / 109 (8.26%)	
occurrences (all)	0	9	
Stomatitis			
subjects affected / exposed	0 / 54 (0.00%)	3 / 109 (2.75%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 54 (1.85%)	24 / 109 (22.02%)	
occurrences (all)	1	24	
Dyspepsia			
subjects affected / exposed	0 / 54 (0.00%)	8 / 109 (7.34%)	
occurrences (all)	0	8	
Vomiting			
subjects affected / exposed	0 / 54 (0.00%)	7 / 109 (6.42%)	
occurrences (all)	0	7	
Renal and urinary disorders			
Creatinine urine abnormal			
subjects affected / exposed	0 / 54 (0.00%)	6 / 109 (5.50%)	
occurrences (all)	0	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 54 (9.26%)	2 / 109 (1.83%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2011	addition of patient diary cards to help with recording participant compliance to the trial medication and drug accountability
03 April 2012	changes to the inclusion/exclusion criteria, changes to the definition of pathway A with regards to collecting baseline biopsies before trial entry, updating the screening process so that HER 2 status can be determined after the patient has been offered the trial, amending the safety reporting section in line with the sponsor SOP along with other minor amendments
13 June 2012	amendments to the protocol, the informed consent form (pathway A and B), the patient information sheet (pathway A and B), the GP letter, the quick summary and the patient diary card and addition of 2 new sites and change of PI at one site
06 September 2012	This amendment relates to the protocol and patient information sheets being updated in line with the annual investigator brochure update. Both the protocol and the patient information sheets have been updated with additional side effects for GDC-0941. The protocol has also been updated so that the Assessment during Treatment section is consistent with the Study Flow Chart section
07 February 2013	This amendment relates to the addition of two new research sites
15 May 2013	This amendment relates to a change in PI at one site
30 May 2013	This amendment relates to the addition of a new research site
26 June 2013	This amendment relates to the addition of two new research sites
24 July 2013	This amendment relates to the addition of two new research sites
23 August 2013	This amendment relates to the addition of a new research site
23 August 2013	This amendment relates to the Patient Information Sheets (pathway A and B) being updated to make the document more patient friendly and relevant to this two week window study
18 September 2013	This amendment relates to the addition of a new research site
18 September 2013	This amendment relates to the change of PI
27 December 2013	This amendment relates to the change of PI
10 June 2014	This amendment relates to the change of PI

08 July 2014	This amendment relates to the change of PI
02 October 2014	This amendment relates to the protocol and the patient information sheets in relation to obtaining verbal informed consent so that the patient can arrive at their first visit in a fasted state to avoid an additional clinic visit.

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/26976426