Clinical trial results:
ALERT: A phase II study of alternating eribulin and hormonal therapy in pre-treated ER+ve breast cancer

Summary

EudraCT number	2014-004112-11
Trial protocol	GB
Global end of trial date	24 July 2018

Results information

Result version number	v1 (current)
This version publication date	01 February 2020
First version publication date	01 February 2020

Trial information

Trial identification

Sponsor protocol code	C/31/2014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02681523
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Du Cane Road, London, United Kingdom, W12 ONN
Public contact	Anna Kasim, Imperial College London, 44 2033130648, alert@imperial.ac.uk
Scientific contact	Anna Kasim, Imperial College London, 44 2033130648, alert@imperial.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	17 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2018
Global end of trial reached?	Yes
Global end of trial date	24 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Eribulin when prescribed in alternating cycles with an Aromatase Inhibitor (AI) in patients with locally advanced or metastatic breast cancer, based on progression free survival (PFS).

Protection of trial subjects:

A Joint Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC) was set up to provide overall supervision for the study and to ensure it was conducted in accordance with Good Clinical Practice (GCP) and provided advice through its independent chairman. The joint TSC/IDMC also monitored the study progress and the committee members met in confidence at regular intervals as they saw fit but at least annually. Following each meeting they reported their findings and recommendations to the chief investigator (CI) and sponsor (CRUK Cancer Clinical Trials Unit) and the Trial Statistician. The joint TSC/IDMC consisted of two clinicians (not entering patients into the study), an independent statistician and an independent chairman, who gave recommendations and decided on continuing or stopping the study, or modifying the protocol.

Background therapy:

Non-Investigational Medicinal Product - Aromatase inhibitors (AIs): anastrozole 1mg, exemestane 25mg or letrozole 2.5mg once daily for 9 weeks.

Evidence for comparator:

Eribulin is standard of care for women with advanced breast cancer. In contrast to premenopausal women, in whom most of the oestrogen is produced in the ovaries, in postmenopausal women oestrogen is mainly produced in peripheral tissues of the body. Because some breast cancers respond to oestrogen, lowering oestrogen production at the site of the cancer (i.e. the adipose tissue of the breast) with AIs has been proven to be an effective treatment for hormone-sensitive breast cancer in postmenopausal women.

AIs work by inhibiting the action of the enzyme aromatase, which converts androgens into oestrogens by a process called aromatization. As oestrogen receptor positive (ER+ve) breast cancers are stimulated by oestrogens, decreasing their production is a way of suppressing recurrence of the breast tumour tissue. The main source of oestrogen is the ovaries in premenopausal women, while in post-menopausal women most of the body's oestrogen is produced in peripheral tissues (outside the central nervous system (CNS)), and also a few CNS sites in various regions within the brain.

Therefore, by alternating eribulin with AIs, we will examine in this pilot study whether there may be breakthrough relapse during the AI therapy or if we can extend the duration that eribulin may be used for. Importantly, blood based biomarkers, the tumour derived fraction of circulating free DNA (ctDNA), and circulating tumour cells will be measured.

Actual start date of recruitment	23 February 2016
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: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single-centre, single arm, open label, non-randomised, phase II pilot study. The study recruited 8 female patients with ER+ve locally advanced or metastatic breast cancer who have received at least one chemotherapy agent in the metastatic setting.

Pre-assignment

Screening details:

Each patient under went a full screening assessment to confirm study eligibility. Patients who met all inclusion criteria (and none of the exclusion criteria) were enrolled onto the study. This included patients who have progressed after at least one chemotherapy regimen for advanced or metastatic disease.

Pre-assignment period milestones

Number of subjects started	8
Number of subjects completed	

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding - open label IMP

Arms

Arm title	Arm 1

Arm description:

Subjects were intravenously administered eribulin 1.23mg/m2 (0.97mg/m2 or 0.62mg/m2 in patients with Child-Pugh A and Child-Pugh B respectively) on day 1 and day 8 of 21 day cycles.

This was then alternated with an AI inhibitor, orally once daily for 9 weeks, followed again by 21 day eribulin cycles and finally a further 9 weeks of the same AI treatment.

Arm type	Experimental
Investigational medicinal product name	Eribulin
Investigational medicinal product code	
Other name	Halaven
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1.23mg/m2 on day 1 and day 8 for every 21 day cycles.

Investigational medicinal product name	Aromatase Inhibitor
Investigational medicinal product code	
Other name	Letrozole, exemestane or anastrozole
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Aromatase inhibitor (NIMP) was prescribed under investigator discretion. Subjects were prescribed either:
Anastrozole 1mg tablets, letrozole 2.5mg tablets or exemestane 25mg tablets.

Number of subjects in period 1	Arm 1
Started	8
Completed	6
Not completed	2
Adverse event, non-fatal	1
Patient non-compliance	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

Thirteen subjects were screened for eligibility and eight of these patients were recruited to the study. Six subsequently completed study and two were withdrawn.

Reporting group values	Overall Trial	Total	
Number of subjects	8	8	
Age categorical			
Subjects aged 18 year and over were included in the study			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	8	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Subjects aged 18 year and over were included in the trial			
Units: years			
median	50		
inter-quartile range (Q1-Q3)	48 to 57	-	
Gender categorical			
Female patients			
Units: Subjects			
Female	8	8	
Male	0	0	
Ethnicity			
Subjects of all ethnicity were included.			
Units: Subjects			
White	6	6	
Turkish	1	1	
Middle Eastern	1	1	
Mixed	0	0	
Asian	0	0	
Black	0	0	
Other ethnic group	0	0	
Eastern Cooperative Oncology Group (ECOG) Performace Status			
An ECOG Performance Assessment was performed for each subject			
Units: Subjects			
ECOG Performance Status 1	4	4	
ECOG Performance Ststus 0	4	4	

ECOG Performance Status 2	0	0	
ECOG Performace Status 3	0	0	
ECOG Performace Status 4	0	0	
ECOG Performance Status 5	0	0	
Smoking Status			
Smoking Status for all subjects were collected			
Units: Subjects			
Never	3	3	
Former	3	3	
Current	1	1	
No Information	1	1	
Tumour Type			
The tumour type for all subjects was assessed using CT or MRI scans of the chest, abdomen and pelvis.			
Units: Subjects			
Invasive Ducal Carcinoma	8	8	
ER Status			
The oestogen receptor status for all subjects was assessed histologically and was ER positive for study enrolment			
Units: Subjects			
Allred	3	3	
Other	5	5	
PgR Status Units: Subjects			
Positive	7	7	
Negative	0	0	
Unknown	1	1	
HER2 Status Units: Subjects			
Zero	5	5	
1+	1	1	
2+	0	0	
3+	0	0	
Not done	2	2	
Primary Tumour Stage Units: Subjects			
Stage I	1	1	
Stage IIA	1	1	
Stage IIIA	1	1	
Stage IIIC	1	1	
No information	4	4	
Primary Tumour Grade Units: Subjects			
G1	1	1	
G2	5	5	
G3	2	2	
Prior Chemotherapy Units: Subjects			
Yes	8	8	
No	0	0	
Prior Radiotherapy Units: Subjects			

Yes	8	8	
No	0	0	
Prior Endocrine Therapy_ Tamoxifen Units: Subjects			
Tamoxifen	8	8	
Prior Surgery Units: Subjects			
Yes	8	8	
No	0	0	
Prior Endocrine Therapy_Exemestane Units: Subjects			
Exemestane	5	5	
No Exemestane	3	3	
Endocrine Therapy_Letrozole and Units: Subjects			
Letrozole	3	3	
Anastrozole	5	5	
Body Mass Index			
Body Mass Index was assessed and reported for all subjects			
Units: kg/m2			
median	26.5		
full range (min-max)	20.3 to 31.6	-	
Primary Tumour Size Units: mm			
median	28		
full range (min-max)	25 to 40	-	

End points

End points reporting groups

Reporting group title	Arm 1

Reporting group description:

Subjects were intravenously administered eribulin 1.23mg/m2 (0.97mg/m2 or 0.62mg/m2 in patients with Child-Pugh A and Child-Pugh B respectively) on day 1 and day 8 of 21 day cycles.

This was then alternated with an AI inhibitor, orally once daily for 9 weeks, followed again by 21 day eribulin cycles and finally a further 9 weeks of the same AI treatment.

Primary: Progression Free Survival (PFS) at fixed time points

End point title	Progression Free Survival (PFS) at fixed time points[1]

End point description:

The median PRS at the end of the study was 235 days. The mean PFS could not be calculated at 3 months, as no patients experienced disease progression at Follow-up.

End point type	Primary

End point timeframe:

PFS rate was measured at fixed time points of 3, 6 and 9 months (as estimated by the Kaplan-Meier Curve).

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: The median Progression-Free Survival (PFS) Rate was calculated based on the time from study enrolment to the first evidence of progression for each patient. Patients were censored at the last follow-up date if they are lost to follow-up, withdrawn from the study or not progressed at the end of the study.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Days				
3 months - cannot be calculated	0			
6 months	202			
9 months	235			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

Only 6 patients had at least one tumour assessment during the study period.

End point type	Secondary

End point timeframe:

Clinical Benefit Rate (CBR), defined as proportion whose best overall response, according Response

Evaluation Criteria in Solid Tumours (RECIST) v1.1, Is either a complete response (CR), partial response (PR) or stable disease (SD) for at least 6 months.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Observed CBR				
Stable disease	3			
Partial response	3			
Complete response	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability

End point title	Safety and Tolerability

End point description:

Safety and tolerability as assessed by adverse events (AE) and serious adverse events (SAEs) according to the Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03)

End point type	Secondary

End point timeframe:

Collected from consent to follow-up for subjects who received at least one dose of study treatment.

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: AE and SAEs				
Mild	71			
Moderate	39			
Severe	17			
Life threatening or disabling	2			
Death	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs and SAEs) were collected from consent to end of follow up for all patients, followed up according to local practice until stabilised or resolved, 9 months.

Adverse event reporting additional description:

All Adverse event were collected electronically in the eCRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Arm1

Reporting group description:

Treatment Arm

Serious adverse events	Arm1		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Ischaemia cerebrovascular			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucositis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Dyspnea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress syndrome			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	6		
Influenza like illness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Mucosal inflammation			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Pain subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 4		
Peripheral swelling subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3		
Pyrexia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3		
Dyspnoea subjects affected / exposed occurrences (all)	4 / 8 (50.00%) 6		
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Pleural effusion subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Tonsillar erythema subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Blood alkaline phosphatase			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood cholesterol increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Grip strength decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			
Ageusia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Dizziness			

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Cognitive disorder			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Abdominal pain			

subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	2			
Ascites				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	4 / 8 (50.00%)			
occurrences (all)	4			
Diarrhoea				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Heartburn/burping				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Melaena				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Mouth ulceration				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	2			
Nausea				
subjects affected / exposed	4 / 8 (50.00%)			
occurrences (all)	4			
Oral pain				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Rectal haemorrhage				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Teeth and gum darkening				

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Teeth and gum thinning			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hepatomegaly			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	6		
Hyperhidrosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin striae			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Muscle spasms			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Pain in jaw			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infections and infestations			
Ear infection			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Neutropenic sepsis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vaginal infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Diabetes mellitus			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2015	Substantial Amendment 01 was made to include the following: • Amendment to the inclusion and exclusion criteria in the number/type of prior lines of therapy and clarification that only site of measurable disease is required. • Change to primary, secondary and translational endpoints • Included action to take in case of pregnancy • Inclusion of serum albumin to biochemistry tests, the removal of troponin I measurement, units of measurements corrected and a change to blood volume collected for translational samples. • Clarification of the location of translational sample analysis • Change from obligatory to optional tissue sample collection • Other minor administrative updates and amendments to wording/typographical errors, including potential risks, the naming of the coordinating centre, change in statistician, updated sponsor details and the change in the naming of the end of study visit.
25 July 2017	Substantial Amendment 02 was made to include the following: • Change in chief investigator (CI) and principal investigator (PI) • Change in contact details for the CI and PI, reflected in the protocol and GP letter. • Administrative updates to reflect staff changes, including the Trial Coordinator, Clinical Trial Manger, Sponsor and member of the Protocol Development Group. • Change to treatment schedule to allow +/- 1 week window for week 18 assessments allowing them to take place during week 19 eribulin treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This was a pilot study planned to recruit 12 patients. Due to slow recruitment, the study was terminated early after the recruitment of 8 patients. Of the patients recruited, 6 completed the study.

Notes: