



Clinical trial results:

Phase II study of ROS1 targeting with crizotinib in advanced E-cadherin negative, ER positive lobular breast cancer, diffuse gastric cancer, triple negative lobular breast cancer or CDH1-mutated solid tumours

Summary

EudraCT number	2017-001680-20
Trial protocol	GB
Global end of trial date	30 August 2024

Results information

Result version number	v1 (current)
This version publication date	31 August 2025
First version publication date	31 August 2025

Trial information

Trial identification

Sponsor protocol code	CCR4684
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03620643
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Royal Marsden NHS Foundation Trust
Sponsor organisation address	Fulham Road , London, United Kingdom, SW3 6JJ
Public contact	ROLO Trial Manager, Royal Marsden - Clinical Trials Unit, ROLO.Trial@rmh.nhs.uk
Scientific contact	ROLO Trial Manager, Royal Marsden - Clinical Trials Unit, ROLO.Trial@rmh.nhs.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	30 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2024
Global end of trial reached?	Yes
Global end of trial date	30 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess confirmed response rate by RECIST 1.1 of crizotinib and fulvestrant in the breast cohort

To assess confirmed response rate by RECIST 1.1 of crizotinib monotherapy in the diffuse gastric cancer, triple negative lobular breast cancer or CDH1-mutated solid tumour (basket) cohort

Protection of trial subjects:

The trial was reviewed by an independent group of people called a Research Ethics Committee to protect the safety, rights, wellbeing and dignity of participants. It received The study favourable opinion by the London – Fulham Research Ethics Committee, confirming the trial met the required ethical standards. In addition, the Medicines and Healthcare products Regulatory Agency (MHRA) approved the use of crizotinib for this study.

All participants provided full informed consent prior to any trial procedures. The eligibility criteria ensured that only patients who were fit for treatment and fully informed could take part. Participant safety monitoring was conducted throughout the trial, including regular hospital visits with clinical examinations to confirm participants remained well enough for continued treatment. All treatment and care of patients during the trial was provided by appropriately trained and delegated staff. Adverse events were collected and monitored continuously to ensure timely identification and management of any safety concerns.

The trial was overseen by an Independent Data Monitoring Committee, a Trial Management Group, a Trial Steering Committee, and a Safety Review Committee. These groups met regularly throughout the conduct of the trial to review safety data and ensure participants were protected at all times during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2019
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: 33
Worldwide total number of subjects	33
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)	24
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study recruited patients between 09/05/2019 and 01/12/2023. Patients were recruited from 5 sites across the United Kingdom; The Royal NHS Foundation Trust, The Christie NHS Foundation Trust, Guys and St Thomas' NHS Foundation Trust, University College London Hospital NHS Foundation Trust and the Beatson West of Scotland Cancer Centre.

Pre-assignment

Screening details:

In the Lobular Breast Cancer Cohort, 32 participants were consented and screened; 5 screen fail, 27 enrolled. In the Basket Cohort, 7 patients were consented and screened; 1 screen fail, 6 enrolled. Screening was based on protocol defined inclusion and exclusion criteria.

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:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Basket cohort

Arm description:

Basket cohort (n=29 participants) will be treated with monotherapy called Crizotinib Oral Capsule [Xalkori] (250 mg b.d) taken on a continuous dosing schedule. One treatment cycle for Crizotinib is 28 days long.

Arm type	Active comparator
Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Basket cohort (n=29 participants) will be treated with monotherapy called Crizotinib Oral Capsule [Xalkori] (250 mg b.d) taken on a continuous dosing schedule. One treatment cycle for Crizotinib is 28 days long.

Crizotinib Oral Capsule [Xalkori]: Crizotinib 250 mg Crizotinib 200mg

Arm title	Lobular Breast Cancer cohort
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Arm description:

Lobular Breast Cancer cohort (n=29 participants) will be treated with combination therapy. The combination therapy includes; Crizotinib Oral Capsule [Xalkori] (250mg b.d.) plus Fulvestrant 50 mg/mL Prefilled Syringe [Faslodex or generic] intramuscular (IM) injection (500 mg per 1 cycle (q28 days, plus loading dose on day 15).

Crizotinib Oral Capsule [Xalkori]: Crizotinib 250 mg Crizotinib 200mg

Fulvestrant 50 MG/ML Prefilled Syringe [Faslodex or generic]: Fulvestrant (Faslodex or generic) is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250mg/5mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure.

Arm type	Active comparator
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Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Arm 2 - Lobular Breast Cancer cohort (n=29 participants) will be treated with combination therapy. The combination therapy includes; Crizotinib Oral Capsule [Xalkori] (250mg b.d.) plus Fulvestrant 50 mg/mL Prefilled Syringe [Faslodex or generic] intramuscular (IM) injection (500 mg per 1 cycle (q28 days, plus loading dose on day 15).

Crizotinib Oral Capsule [Xalkori]: Crizotinib 250 mg Crizotinib 200mg

Fulvestrant 50 MG/ML Prefilled Syringe [Faslodex or generic]: Fulvestrant (Faslodex or generic) is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250mg/5mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Arm 2 - Lobular Breast Cancer cohort will be treated with combination therapy. The combination therapy includes; Crizotinib Oral Capsule [Xalkori] (250mg b.d.) plus Fulvestrant 50 mg/mL Prefilled Syringe [Faslodex or generic] intramuscular (IM) injection (500 mg per 1 cycle (q28 days, plus loading dose on day 15).

Crizotinib Oral Capsule [Xalkori]: Crizotinib 250 mg Crizotinib 200mg

Fulvestrant 50 MG/ML Prefilled Syringe [Faslodex or generic]: Fulvestrant (Faslodex or generic) is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250mg/5mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure.

Number of subjects in period 1	Basket cohort	Lobular Breast Cancer cohort
Started	6	27
Completed	6	27

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	33	33	
Age categorical			
Units: Subjects			
Adults (18-64 years)	24	24	
From 65-84 years	9	9	
Age continuous			
Units: years			
median	57		
full range (min-max)	35 to 83	-	
Gender categorical			
Units: Subjects			
Female	33	33	
Male	0	0	
Menopausal Status			
Units: Subjects			
Peri-menopausal	5	5	
Post-menopausal	24	24	
Pre-menopausal	4	4	
Cancer			
Units: Subjects			
ER positive/HER2 negative Lobular breast cancer	27	27	
Diffuse gastric cancer	1	1	
Triple negative lobular breast cancer	5	5	
other CDH1 mutated cancer	0	0	

End points

End points reporting groups

Reporting group title	Basket cohort
Reporting group description: Basket cohort (n=29 participants) will be treated with monotherapy called Crizotinib Oral Capsule [Xalkori] (250 mg b.d) taken on a continuous dosing schedule. One treatment cycle for Crizotinib is 28 days long.	
Reporting group title	Lobular Breast Cancer cohort
Reporting group description: Lobular Breast Cancer cohort (n=29 participants) will be treated with combination therapy. The combination therapy includes; Crizotinib Oral Capsule [Xalkori] (250mg b.d.) plus Fulvestrant 50 mg/mL Prefilled Syringe [Faslodex or generic] intramuscular (IM) injection (500 mg per 1 cycle (q28 days, plus loading dose on day 15). Crizotinib Oral Capsule [Xalkori]: Crizotinib 250 mg Crizotinib 200mg Fulvestrant 50 MG/ML Prefilled Syringe [Faslodex or generic]: Fulvestrant (Faslodex or generic) is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250mg/5mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure.	

Primary: Percentage of Breast Cancer Cohort Participants With Objective Response Assessed Using RECIST v1.1

End point title	Percentage of Breast Cancer Cohort Participants With Objective Response Assessed Using RECIST v1.1 ^{[1][2]}
End point description: To assess confirmed response rate by RECIST 1.1 of crizotinib and fulvestrant in advanced E-cadherin negative, ER positive lobular breast cancer.	
End point type	Primary
End point timeframe: From Day 1 to Progressive Disease, assessed up to end of study (up to approximately 48 months)	

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: N/A - Descriptive statistical analyses only

[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: N/A - Descriptive statistical analyses only

End point values	Lobular Breast Cancer cohort			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Participants	1			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Basket Cohort Participants With Objective Response Assessed Using RECIST v1.1

End point title	Percentage of Basket Cohort Participants With Objective Response Assessed Using RECIST v1.1 ^[3] ^[4]
End point description: To assess confirmed response rate by RECIST 1.1 of crizotinib monotherapy in advanced E-cadherin negative, diffuse gastric cancer, triple negative lobular breast cancer or CDH1-mutated solid tumour.	
End point type	Primary
End point timeframe: From Day 1 to Progressive Disease, assessed up to end of study (up to approximately 48 months)	

Notes:

[3] - 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: N/A - Descriptive statistical analyses only

[4] - 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: N/A - Descriptive statistical analyses only

End point values	Basket cohort			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs) and Serious AEs (SAEs)

End point title	Percentage of Participants With Adverse Events (AEs) and Serious AEs (SAEs)
End point description: To assess the overall safety and tolerability of crizotinib with fulvestrant in the breast cancer cohort and as monotherapy in the basket cancer cohort. Toxicity will be assessed by CTCAE (version 4) every 4 weeks during study treatment. Adverse events, including serious adverse events, will be recorded until 30 days after the last dose of study treatment with crizotinib.	
End point type	Secondary
End point timeframe: From Day 1 to 90 days after last dose of study drug, assessed up to end of study (up to approximately 45 months)	

End point values	Basket cohort	Lobular Breast Cancer cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	27		
Units: Participants	6	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Assessed Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECISTv1.1) in Both Basket and Breast Cancer Cohorts

End point title	Progression-free Survival (PFS) Assessed Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECISTv1.1) in Both Basket and Breast Cancer Cohorts
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End point description:

PFS is defined as the time from baseline treatment to the first occurrence of PD, as determined by the investigator using RECIST v1.1, or death from any cause during the study, whichever occurs first. PD is defined as greater than or equal to ($\geq$) 20 percent (%) relative increase and $\geq$ 5 millimeter (mm) of absolute increase in the sum of diameters (SD) of target lesions (TLs), taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions.

End point type	Secondary
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End point timeframe:

From Day 1 to disease progression (PD) or death from any cause, assessed up to end of study (up to approximately 48 months)

End point values	Basket cohort	Lobular Breast Cancer cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[5]	27		
Units: Participants				
median (confidence interval 95%)	1.8 (0.5 to 99999999)	1.8 (1.1 to 3.2)		

Notes:

[5] - The upper limit of the 95% confidence interval was not reached, '99999' entered as a placeholder

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Overall Survival in Each Cohort

End point title	Assessment of Overall Survival in Each Cohort
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End point description:

Overall survival, calculated from day 1 of study treatment to the date of death from any cause.

End point type	Secondary
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End point timeframe:

From Day 1 to disease progression (PD) or death from any cause, assessed up to end of study (up to approximately 48 months)

End point values	Basket cohort	Lobular Breast Cancer cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[6]	27		
Units: Participants				
median (confidence interval 95%)	4.4 (1.3 to 99999999)	17.5 (6.9 to 26.0)		

Notes:

[6] - The upper limit of the 95% confidence interval was not reached; '99999' entered as a placeholder

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE and AE collection commenced at the time the first patient provided their written informed consent to participate in the trial and continued until 28 days after the last administration of crizotinib or fulvestrant (IMP).

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Basket cohort
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Reporting group description:

Basket cohort (n=29 participants) will be treated with monotherapy called Crizotinib Oral Capsule [Xalkori] (250 mg b.d) taken on a continuous dosing schedule. One treatment cycle for Crizotinib is 28 days long.

Reporting group title	Lobular Breast Cancer cohort
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Reporting group description:

Lobular Breast Cancer cohort (n=29 participants) will be treated with combination therapy. The combination therapy includes; Crizotinib Oral Capsule [Xalkori] (250mg b.d.) plus Fulvestrant 50 mg/mL Prefilled Syringe [Faslodex or generic] intramuscular (IM) injection (500 mg per 1 cycle (q28 days, plus loading dose on day 15).

Crizotinib Oral Capsule [Xalkori]: Crizotinib 250 mg Crizotinib 200mg

Fulvestrant 50 MG/ML Prefilled Syringe [Faslodex or generic]: Fulvestrant (Faslodex or generic) is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250mg/5mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure.

Serious adverse events	Basket cohort	Lobular Breast Cancer cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	5 / 27 (18.52%)	
number of deaths (all causes)	6	20	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fracture	Additional description: Fractured rib		
subjects affected / exposed	1 / 6 (16.67%)	0 / 27 (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			
Fever			

subjects affected / exposed	0 / 6 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer	Additional description: Oesophageal ulceration		
subjects affected / exposed	1 / 6 (16.67%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ascites			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 6 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	0 / 6 (0.00%)	1 / 27 (3.70%)	
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	Basket cohort	Lobular Breast Cancer cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	27 / 27 (100.00%)	
Vascular disorders			
Hot flashes			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	1 / 6 (16.67%)	3 / 27 (11.11%)	
occurrences (all)	4	8	
Edema trunk			
subjects affected / exposed	2 / 6 (33.33%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	12 / 27 (44.44%)	
occurrences (all)	1	15	
Pain			
subjects affected / exposed	1 / 6 (16.67%)	2 / 27 (7.41%)	
occurrences (all)	1	4	
Fever			
subjects affected / exposed	0 / 6 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Flu like symptoms			
subjects affected / exposed	0 / 6 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	

Localised edema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 27 (7.41%) 5	
Other subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 10	7 / 27 (25.93%) 12	
Respiratory, thoracic and mediastinal disorders			
Dyspnea subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 4	2 / 27 (7.41%) 2	
Pleural effusion subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	0 / 27 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	6 / 27 (22.22%) 7	
Sore throat subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 27 (7.41%) 2	
Other subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 4	1 / 27 (3.70%) 1	
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 27 (7.41%) 2	
Investigations			
Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 27 (0.00%) 0	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 5	17 / 27 (62.96%) 29	
Alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	9 / 27 (33.33%) 11	

Aspartate aminotransferase increased			
subjects affected / exposed	4 / 6 (66.67%)	20 / 27 (74.07%)	
occurrences (all)	5	42	
Creatinine increased			
subjects affected / exposed	2 / 6 (33.33%)	4 / 27 (14.81%)	
occurrences (all)	2	4	
Lymphocyte count decreased			
subjects affected / exposed	2 / 6 (33.33%)	4 / 27 (14.81%)	
occurrences (all)	4	7	
GGT increased			
subjects affected / exposed	0 / 6 (0.00%)	6 / 27 (22.22%)	
occurrences (all)	0	10	
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	5 / 27 (18.52%)	
occurrences (all)	0	6	
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	4	
White blood cell decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	3	
Other			
subjects affected / exposed	0 / 6 (0.00%)	6 / 27 (22.22%)	
occurrences (all)	0	24	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 27 (14.81%)	
occurrences (all)	0	6	
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 6 (33.33%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Dizziness			

subjects affected / exposed	0 / 6 (0.00%)	8 / 27 (29.63%)	
occurrences (all)	0	10	
Headache			
subjects affected / exposed	0 / 6 (0.00%)	6 / 27 (22.22%)	
occurrences (all)	0	6	
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Other			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 6 (16.67%)	12 / 27 (44.44%)	
occurrences (all)	1	21	
Other			
subjects affected / exposed	1 / 6 (16.67%)	3 / 27 (11.11%)	
occurrences (all)	1	26	
Eye disorders			
Flashing lights			
subjects affected / exposed	1 / 6 (16.67%)	4 / 27 (14.81%)	
occurrences (all)	2	4	
Blurred vision			
subjects affected / exposed	0 / 6 (0.00%)	5 / 27 (18.52%)	
occurrences (all)	0	5	
Other			
subjects affected / exposed	0 / 6 (0.00%)	4 / 27 (14.81%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 6 (16.67%)	3 / 27 (11.11%)	
occurrences (all)	1	4	
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	8 / 27 (29.63%)	
occurrences (all)	3	10	
Ascites			

subjects affected / exposed	1 / 6 (16.67%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	2 / 6 (33.33%)	10 / 27 (37.04%)	
occurrences (all)	2	11	
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	13 / 27 (48.15%)	
occurrences (all)	1	21	
Gastric ulcer			
subjects affected / exposed	1 / 6 (16.67%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal pain			
subjects affected / exposed	2 / 6 (33.33%)	2 / 27 (7.41%)	
occurrences (all)	4	3	
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	20 / 27 (74.07%)	
occurrences (all)	1	29	
Obstruction gastric			
subjects affected / exposed	1 / 6 (16.67%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)	18 / 27 (66.67%)	
occurrences (all)	2	30	
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Bloating			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	3	
Other			
subjects affected / exposed	2 / 6 (33.33%)	3 / 27 (11.11%)	
occurrences (all)	2	5	
Skin and subcutaneous tissue disorders			
Other			
subjects affected / exposed	1 / 6 (16.67%)	3 / 27 (11.11%)	
occurrences (all)	1	3	

Musculoskeletal and connective tissue disorders Chest wall pain subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Other subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1	 0 / 27 (0.00%) 0 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Other subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Hypoalbuminemia subjects affected / exposed occurrences (all) Hyponatremia subjects affected / exposed occurrences (all) Hypercalcaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	 3 / 27 (11.11%) 3 4 / 27 (14.81%) 6 5 / 27 (18.52%) 6 3 / 27 (11.11%) 3 3 / 27 (11.11%) 3 2 / 27 (7.41%) 2	

Hyperkalemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2019	Addition of overall survival (OS) as a secondary endpoint. Addition of CA125 testing for lobular breast patients added into the amended protocol (in text and schedule of events table) as it is frequently a more useful tumour marker than CA15-3 for patients with peritoneal disease. Removal of prior fulvestrant as an exclusion criterion. The Schedule of Events table amended to include: • An extra CA125 test (for Breast patients). • A "Survival follow-up (every 6 months)" column and row.
01 October 2020	Renaming of the gastric cancer cohort to a basket cohort that also includes triple negative lobular breast cancer or CDH1-mutated solid tumour patients. Addition of inclusion criterion for E-cadherin negative patients in both the breast and basket cohorts. Amendment to pregnancy prevention guidance following update to SmPC for fulvestrant IMP.
17 February 2022	Following meetings of the Independent Data Monitoring Committee and Trial Steering Committee, it was recommended to open up the inclusion criteria to improve recruitment by including a CDK4/6 inhibitor as a previous line of therapy for lobular breast cancer patients instead of only a line of chemotherapy. Other substantial changes made for reporting of adverse events for abnormal laboratory values, off-site procedures being allowed due to emergency situations such as COVID-19 and instructions added for the management of non haematological toxicities
20 February 2023	Amendment to patient information sheet and study RSI following updated SmPC for Crizotinib.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported