ROLo: Phase II study of **RO**S1 targeting with crizotinib in advanced E-cadherin negative, ER positive **lo**bular breast cancer, diffuse gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumours

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KEY CONTACTS

Chief Investigator	Dr Alicia Okines Consultant Medical Oncologist The Royal Marsden NHS Foundation Trust Breast Cancer Unit Fulham Road, London SW3 6JJ Tel: 020 7352 8171 Email: Alicia.Okines@rmh.nhs.uk
Lead Co-Investigator (Breast cancer)	Professor Nicholas Turner Consultant in Medical Oncologist The Royal Marsden NHS Foundation Trust Breast Cancer Unit Fulham Road, London SW3 6JJ Telephone: 020 78118914 Email: Nick.Turner@icr.ac.uk
Sponsor	The Royal Marsden NHS Foundation Trust Downs Road Sutton SM2 5PT Sponsor contact: Ann Gandolfi Clinical R&D Manager Email: Ann.Gandolfi@rmh.nhs.uk
RM CTU Clinical Trial Coordinator	ROLo Trial Manager Royal Marsden Clinical Trials Unit The Royal Marsden NHS Foundation Trust Telephone: 0208 915 6506 Email: ROLo.trial@rmh.nhs.uk
Study statistician	Kabir Mohammed RDSU, The Royal Marsden NHS Foundation Trust Downs Road, Sutton, SM2 5PT Tel: 02031865048 Email: kabir.mohammed@rmh.nhs.uk
Lead Co-investigator (Translational research)	Professor Christopher Lord Team Leader and Reader in Cancer Genomics and Therapeutics, The Breast Cancer Now Toby Robins Breast Cancer Research Centre, The Institute of Cancer research, London, SW3 6JB, UK Tel: 020 7153 5190 Email: Chris.Lord@icr.ac.uk
Lead Co-Investigator (Gastric cancer)	Dr Naureen Starling Consultant Medical Oncologist The Royal Marsden NHS Foundation Trust Fulham Road, London SW3 6JJ Tel: 020 7352 8171 Email: Naureen.Starling@rmh.nhs.uk

PARTICIPATING INVESTIGATORS AND SITES

	Principal Investigator	Site address
Site 1 :	Dr Alicia Okines Consultant Medical Oncologist Tel: 020 8118100 Email: Alicia.okines@rmh.nhs.uk	The Royal Marsden NHS Foundation Trust Fulham Road, London SW3 6JJ & Downs Road, Sutton SM2 5PT
Site 2:	Dr Anne Armstrong Consultant Medical Oncologist Tel: 0161 446 8138 Email: anne.armstrong3@nhs.net	The Christie NHS Foundation Trust Derek Crowther Clinical Trials Unit Wilmslow Road Manchester, M20 4BX
Site 3:	Professor Elinor Sawyer Consultant Medical Oncologist Tel: 02071884244 Email: elinor.sawyer@kcl.ac.uk	Guys and St Thomas' NHS Foundation Trust Guys Hospital, Great Maze Pond, London, SE1 9RT
Site 4:	Dr Rebecca Roylance Consultant Medical Oncologist Tel: 020 3447 9072 Email: Rebecca.Roylance@uclh.nhs.uk	UCLH NHS Foundation Trust University College Hospital, 235 Euston Road, London, NW1 2BU
Site 5:	Professor Carlo Palmieri Consultant Medical Oncologist Tel: 0151 794 9813 Email: C.Palmieri@liverpool.ac.uk	Clatterbridge Cancer Centre NHS Foundation Trust Clatterbridge Road, Bebington, Wirral, CH63 4JY
Site 6	Dr Iain Macpherson Consultant Medical Oncologist Tel: 0141 301 7000 Email: Iain.MacPherson@glasgow.ac.uk	Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow, Scotland. G12 0YN
Site 7	Dr Madeleine Hewish Consultant Medical Oncologist Tel: 01483 571122 Madeleine.hewish@nhs.net	St Luke's Cancer Centre, Royal Surrey NHS Foundation Trust, Egerton Road, Guildford, GU2 7XX

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	ABPI	Association of the British Pharmaceutical Industry
	AE	Adverse event
	Alk phos	Alkaline phosphatise
	ALT	Alanine aminotransferase
	ANC	Absolute neutrophil count
	AST	Aspartate aminotransferase
B	BP	Blood pressure
	BSA	Body surface area
C	^{0}C	Degrees Celsius
	CI	Chief Investigator
	CIRB	Central Institutional Review Board
	CR	Complete response
	CRA	Clinical Research Associate
	CRF	Case report form
	CT	Computerised tomography
	CTA	Clinical trial authorisation
	CTC	Clinical Trial Coordinator
	CTCAE	Common Terminology Criteria for Adverse Events
	ctDNA	Circulating tumour DNA
	CTU	Clinical Trials Unit
D	Day	Calendar day
	DCF	Data clarification form
E	ECG	Electrocardiogram
	EPD	Early progressive disease
F	FDG	Fluorodeoxyglucose
G	GCP	Good Clinical Practice
	g/dL	Gram(s) per decilitre
	GMP	Good Manufacturing Practice
	GTAC	Gene Therapy Advisory Committee
H	Hb	Haemoglobin
	HR	Hazard Ratio
	HCG	Human chorionic gonadotropin
	HIV	Human immunodeficiency virus
I	ICH GCP	International Conference on Harmonisation of Good Clinical Practice

	IHC	Immunohistochemistry
	IMP	Investigational medicinal product
	ITF	Investigator Trial File
L	LVEF	Left ventricular ejection fraction
M	mg/m^2	Milligram per square metre
	MHRA	Medicines and Healthcare products Regulations Agency
	MRI	Magnetic resonance imaging
N	NCI	National Cancer Institute
P	PD	Progressive disease
	PET	Positron emission tomography
	PI	Principal Investigator
	PK	Pharmacokinetic
	PR	Partial response
	PRP	Platelet-rich plasma
Q	QC	Quality control
	QP	Qualified Person
R	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumours
	RM	Royal Marsden
S	SAE	Serious adverse event
	SD	Stable disease
	SGDCF	Site generated data clarification form
	SDV	Source data verification
	SOP	Standard operating procedure
	SPC	Summary of Product Characteristics
	SUSAR	Suspected unexpected serious adverse (drug) reaction
U	ULN	Upper limit of normal
	USM	Urgent safety measure
W	WFI	Water for Injection
	WBC	White blood cell
	WHO	World Health Organisation

PROTOCOL SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:	
Signature:	Date: ...../...../.....
Name (please print): Dr Alicia Okines	
Lead Co-Investigator:	
Signature:	Date: ...../...../.....
Name: (please print): Professor Nicholas Turner	
Statistician:	
Signature:	Date: ...../...../.....
Name: (please print): **K**abir Mohammed	

INVESTIGATOR SIGNATURE

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki (Appendix 2), the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and to ensure that all staff members are aware of their clinical trial responsibilities.

INVESTIGATOR'S NAME:	
SIGNATURE:	
DATE:	

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

1. PROTOCOL SUMMARY

1.1 Primary objectives and endpoints

Primary objective	Endpoint
To assess confirmed response rate by RECIST 1.1 of crizotinib and fulvestrant in the breast cohort	Confirmed response rate, by RECIST 1.1, of crizotinib and fulvestrant in advanced E-cadherin negative, ER positive lobular breast cancer
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	Confirmed response rate, by RECIST 1.1, of crizotinib in advanced E-cadherin negative, diffuse gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumour.

1.2 Secondary objectives and endpoints

Secondary objectives	Endpoints
To assess the overall safety and tolerability of crizotinib with fulvestrant in the breast cancer cohort and as monotherapy in the gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumour (basket) cohort.	Overall safety and tolerability of crizotinib with Fulvestrant. 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.
To assess the clinical benefit rate (response and stable disease lasting at least 24 weeks) in the breast cancer cohort	Clinical benefit rate (response or stable disease lasting at least 24 weeks), assessed by RECIST 1.1 by local radiology review.
To assess progression-free survival in each cohort	Progression-free survival, calculated from day 1 of study treatment to the date of radiological disease progression or death from any cause.
To assess overall survival in each cohort	Overall survival, calculated from day 1 of study treatment to the date of death from any cause.

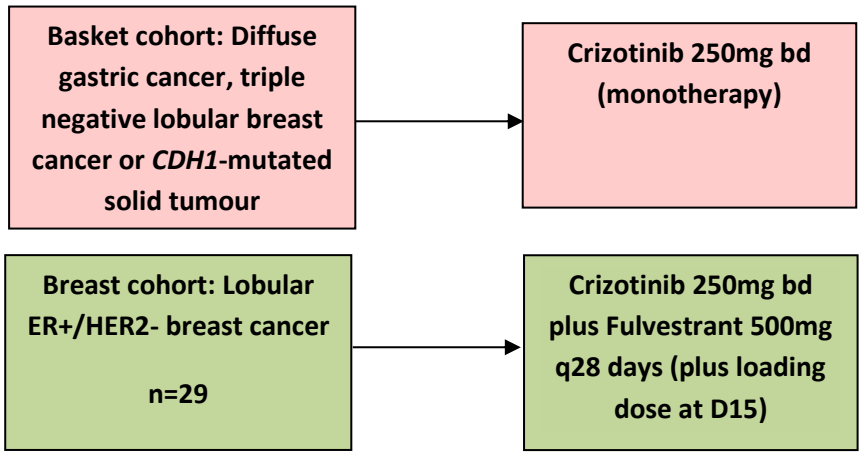
1.3 Exploratory objectives and endpoints

Exploratory objectives	Endpoints
To assess the objective response rate in centrally confirmed E-Cadherin negative and *CDH1* mutated tumours	Objective response rate in centrally confirmed E-cadherin negative and *CDH1* mutated tumours
To evaluate candidate predictive biomarkers of sensitivity or resistance to crizotinib in each cohort, including but not limited to tumour Ki67, E-cadherin expression, *MET* gene copy number *CDH1* mutation status, *PIK3CA* and *ESR1* mutations	Objective response rate in patients with *PIK3CA*, *ESR1*, and *CDH1* mutations or *MET* amplification in baseline plasma DNA
To explore the predictive and/or pharmacodynamic characteristics of peripheral blood and additional tumour tissue biomarkers that may be relevant to the mechanism of action of or resistance to crizotinib.	Exploratory assessment of biomarkers of response in baseline tumour biopsy, and of acquired resistance in progression biopsies and plasma DNA.

1.4 Design

Multi-centre study design, recruitment over 36 months from up to 8 high volume centres including the Royal Marsden. Parallel recruitment to breast and basket cohorts.

Breast cohort treated with crizotinib and fulvestrant, basket cohort treated with crizotinib monotherapy.



1.5 Administration schedule

This is a phase II trial combining the ALK/ROS1 inhibitor crizotinib with the selective oestrogen receptor degrader, fulvestrant in advanced lobular breast cancer and of crizotinib monotherapy in advanced diffuse gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumours.

1.6 Treatment group

Patients with histological confirmation of E-cadherin negative, previously treated advanced lobular breast cancer or diffuse gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumours.

1.7 Trial timelines and accrual rate

A maximum of 29 breast cancer and 29 gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumour patients will be enrolled

The anticipated accrual rate is 2 breast cancer and 2 gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumour patients per month across up to 8 centres. It is anticipated that the duration of recruitment to the study will be 36 months.

1.8 Role of study sponsor and funder

For this trial some of the duties of the sponsor have been delegated to the Chief Investigator (CI), for example the CI has overall responsibility for the design and development of the protocol. The sponsorship agreement describes the allocation of such responsibilities, and a summary of this can be provided by the sponsor upon request.

Breast Cancer Now and Pfizer are providing funding for the study. Neither party contributed to the design or protocol development, but both parties independently reviewed the protocol during development.

Neither Pfizer nor BCN will be involved in the conduct of the study, data analysis or interpretation, but both parties will be provided with study reports prior to submission for presentation and publication.

2. INTRODUCTION

2.1 Background

2.1.1 Lobular breast cancer

Lobular breast cancers are characterised by loss of function of the cell adhesion molecule, E-cadherin, due to mutations or epigenetic alterations in the tumour suppressor gene *CDH1* [1]. In addition to the roles of E-cadherin in cell architecture and migration, the protein also appears to mediate signalling through EGFR and the Wnt pathway [2, 3]. Lobular cancers are typically ER and PgR positive and HER2 negative [3], have a luminal A intrinsic subtype; as such hormonal therapy is the mainstay of treatment for advanced lobular breast cancer before chemotherapy is necessary after the development of resistance. Lobular breast cancers respond less well to chemotherapy than ductal carcinomas [4], therefore there is a real need to develop new agents for patients with disease progression despite prior hormonal therapy. There are currently no recruiting studies worldwide investigating novel therapies specifically for advanced lobular breast cancer patients.

2.1.2 Diffuse gastric cancer

Diffuse gastric cancers are similarly characterised by loss of function of the cell adhesion molecule, E-cadherin, either due to germline mutations in *CDH1* in the case of hereditary diffuse gastric cancer, or hypermethylation in the *CDH1* promoter region in sporadic ally occurring forms of the disease[5].

Diffuse gastric cancer is often poorly chemotherapy responsive but was commonly treated with standard first-line platinum-based chemotherapy, and second-line taxane-based chemotherapy. The introduction of the peri-operative platinum and taxane-containing FLOT regimen[6] has left many patients without a chemotherapy option following relapse. The optimal treatment for this sub-type of gastric cancer remains controversial [7]. Although MET expression is common (39% in one study), *MET* gene amplification is reported in less than 10% of all gastric cancers, and 15% of the diffuse sub-type[8] *FGFR2* amplification is present in a further 10% of cases[9].

2.1.3 Triple negative lobular breast cancer

Approximately 15% of invasive lobular carcinomas (ILC) are ER negative at the time of breast cancer diagnosis, or at relapse due to loss of ER expression. Like triple negative invasive ductal cancers (IDC), triple negative ILC are associated with an inferior prognosis compared to ER positive/HER2 negative disease [16]. However, outcomes are similar to those expected for triple negative IDC [17].

E-cadherin loss is diagnostic of all subtypes of lobular breast cancer, including those which are ER negative. Despite being “triple negative,” in contrast to triple negative IDC, these uncommon ILC are usually luminal A or B and rarely basal intrinsic subtype [18, 19].

2.1.4 *CDH1*-mutated solid tumours

A large study of over 5000 tumour samples has described *CDH1* mutations in skin, bladder, colorectal, endometrial, oesophageal, renal, lung, ovarian, prostate and thyroid cancers [20].

2.2 Investigational medicinal products

2.2.1 Crizotinib

Crizotinib is a small molecule inhibitor of the Anaplastic lymphoma kinase (ALK) receptor tyrosine kinase, the hepatic growth factor receptor (c-Met) and ROS1, which is licensed in ALK-positive advanced non-small cell lung cancer (NSCLC). The recommended dose schedule is 250mg bd taken on a continuous dosing schedule.

2.2.1.1 Crizotinib clinical experience

An open-label phase III trial of crizotinib compared to chemotherapy in patients with advanced ALK-positive non-squamous, NSCLC reported significant prolongation of progression-free survival (PFS) with crizotinib (median, 10.9 months vs. 7.0 months; hazard ratio (HR) for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001). Objective response rates were also increased with crizotinib (74% and 45%, respectively (P<0.001). median overall survival has not been reached, but 1-year overall survival was 84% with crizotinib and 79% with chemotherapy. The most common adverse events with crizotinib were vision disorders, gastrointestinal toxicity (diarrhoea, nausea), and oedema [10].

A single-arm study in NSCLC patients with ROS-1 re-arrangements also demonstrated promising efficacy from crizotinib; the objective response rate was 72%, median PFS was 19.2 months (95% CI, 14.4 to not reached), and no new safety signals were observed [11].

In advanced gastro-oesophageal cancer, four patients with MET amplification (measured by fluorescent in situ hybridisation) were treated with crizotinib, of whom two (50%) experienced tumour shrinkage[12]. Crizotinib has not been previously investigated in patients with breast cancer.

2.2.1.2 Crizotinib Pharmacokinetic Drug Interactions

Co-administration of crizotinib with strong CYP3A inhibitors may increase plasma crizotinib concentrations. Therefore, concomitant use of such medications or grapefruit juice must be avoided.

Co-administration of crizotinib with strong CYP3A inducers may reduce crizotinib plasma concentrations, so concomitant use of such medications must be avoided.

Co-administration of crizotinib with agents which increase gastric pH (proton pump inhibitors, H2 blockers, antacids) results in a minor reduction in crizotinib total exposure, so should be avoided unless clinically necessary. No adjustment to the starting dose of crizotinib is required in patients taking medications which increase gastric pH.

Crizotinib is a moderate inhibitor of CYP3A and CYP2B6 and a weak inhibitor of UGT1A1, UGTB7, OCT1 and OCT2, so may increase plasma concentrations of drugs which are substrates of these enzymes (such as alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, tacrolimus (CYP 3A), bupropion and efavirenz (CYP 2B6), raltegravir, irinotecan (UGT1A1), morphine, naloxone (UGT2B7), metformin, procainamide (OCT 1 and 2)).

Crizotinib may inhibit intestinal P-gp, therefore co-administration with substrates of P-gp (such as digoxin, dabigatran, colchicine and pravastatin) may increase their therapeutic effect and toxicity.

Concomitant administration of crizotinib with oral contraceptives may be reduced.

2.2.1.3 Crizotinib Pharmacodynamic drug interactions

Prolonged QT interval is observed with crizotinib; therefore concomitant administration with other medications known to prolong QT or induce Torsades de pointes is not permitted.

Bradycardia has been reported with crizotinib, therefore use with other agents which can induce bradycardia (verapamil, diltiazem, beta-blockers, digoxin) should be avoided.

2.2.1.4 Crizotinib and fulvestrant

The selective estrogen receptor degrader (SERD) fulvestrant is an active hormonal therapy that inhibits and degrades the estrogen receptor, with anti-tumour activity in cancers that have progressed on prior endocrine therapy. Crizotinib has never been combined with fulvestrant clinically; however there are no overlapping toxicities. A phase I study of crizotinib in combination with a different endocrine therapy, the non-steroidal anti-androgen, enzalutamide, reported no dose-limiting toxicities from the combination[13].

2.2.2 Compatible adverse event profiles

The dose limiting toxicities (DLT) in the phase I trial of Crizotinib were grade 3 transaminitis at the 200mg od dose level and grade 3 fatigue in 2 patients at 300mg bd. The maximum tolerated dose was established as 250mg bd [14].

There were no reported DLTs for fulvestrant (Howell et al., Lancet 1995), but dosing is limited by the volume acceptable for IM injection. The CONFIRM trial necessitated two 5ml IM injections to deliver the monthly 500mg dose [15].

The adverse event profiles suggest that each combination has the potential to be well tolerated, with non-overlapping DLT.

3. RATIONALE FOR THE PROPOSED TRIAL

Despite their characteristic defects in E-cadherin, there have been few clinical trials that have focused on invasive lobular breast cancers (ILCs), with ILC generally forming a small subgroup of ER+ breast cancer studies. This is because efforts to identify specific therapeutic targets associated with loss of E-cadherin expression, the pathognomic alteration in this breast cancer subtype, have to date been limited to synthetic lethal screens in a non-tumour breast epithelial cell line model, MCF10A[16]. This particular effort identified crizotinib, a ROS1/MET/ALK inhibitor as selectively targeting this E-cadherin defective non-tumour epithelial cell line. However from this data it was not clear whether actionable/druggable E-cadherin synthetic lethal effects could be identified that operated in E-cadherin defective breast tumour cells and in *in vivo* models of E-cadherin defective breast cancer. Furthermore it was not clear that actionable E-cadherin synthetic lethal effects could be identified that still operated in the face of the considerable molecular heterogeneity seen in human cancers.

To model breast cancers with loss of E-cadherin, the Lord Lab (ICR, London) used CRISPR-Cas9 mutagenesis in MCF7 breast tumour cells (ER-positive, luminal A, *PIK3CA* mutant; described hereafter as $MCF7^{Parental}$ cells) to generate daughter clones, $MCF7^{A02}$, $MCF7^{B04}$ and $MCF7^{B05}$, with frameshift mutations in *CDH1* and loss of E-cadherin expression (Fig. 1A). Compared to $MCF7^{Parental}$ cells, E-cadherin defective cells displayed a rounded morphology seen in breast tumour cells harbouring naturally occurring E-cadherin mutations. $MCF7^{A02}$ and $MCF7^{Parental}$ cells were used in two parallel functional screens to identify E-cadherin synthetic lethal effects: (i) a drug sensitivity screen where the relative sensitivity of cells to an in–house curated library of 80 small-molecule inhibitors was assessed and (ii) a parallel siRNA sensitivity screen targeting >1000 cell cycle control genes, kinase-coding genes or DNA repair related genes. The drug sensitivity screens identified a series of candidate E-cadherin synthetic lethal drugs, including the ROS1/MET/ALK inhibitors crizotinib (PF02341066, Pfizer) and foretinib (GSK1363089, GSK) (Fig. 1B). The siRNA screens identified a series of candidate synthetic lethal effects including ROS1 (ROS Proto-Oncogene 1, Receptor Tyrosine Kinase, Fig. 1C). This raised the possibility that the synthetic lethality between ROS1 and E-cadherin in E-cadherin defective cells might be exploited by the use of ROS1 inhibitors such as crizotinib and foretinib. In validation experiments, each of the four individual ROS1 siRNAs from the ROS1 SMARTpool caused silencing of ROS1 and preferentially inhibited the E-cadherin deficient $MCF7^{A02}$ clone and also an E-cadherin defective MCF10A $CDH1^{-/-}$ non-tumour cell line (data not shown). Two further E-cadherin defective clones from the MCF7 CRISPR-Cas9 targeting, $MCF7^{B04}$ and $MCF7^{B05}$, were also significantly more sensitive to either foretinib or crizotinib than the parental cells (data not shown). Restoring E-cadherin expression in $MCF7^{A02}$ using a Flag-epitope tagged E-cadherin cDNA expression construct reduced foretinib sensitivity as well as sensitivity to an additional ROS1/MET/ALK inhibitor, TAE673 (data not shown), confirming that E-cadherin influences the response to these agents. In assessing the effects of additional ROS1/MET/ALK inhibitors on E-cadherin isogenic cells, foretinib and crizotinib were found to give the greatest difference in drug sensitivity between E-cadherin wild type and defective cells (Fig. 1D), warranting their further investigation. The sensitivity of E-cadherin defective cells to foretinib was similar to that observed in HCC78 cells (Fig. 1E), which harbour a *SLC34A2-ROS1* gene fusion rearrangement rendering the cell line highly addicted to ROS1 kinase activity. E-cadherin defective cells were also more sensitive to a recently described ROS1 kinase inhibitor, PF-06463922 (lorlatinib) (Fig. 1F). Transfection of E-cadherin defective $MCF7^{A02}$ cells with increasing amounts of ROS1 siRNA enhanced the cell inhibitory effects of foretinib (Fig. 1G), whereas expression of a crizotinib-refractory p.G2032R mutant *ROS1* fusion cDNA caused crizotinib resistance in E-cadherin

defective cells (data not shown), suggesting that ROS1 could be a critical foretinib target in E-cadherin defective cells. To assess whether the synthetic lethal effect of ROS1 inhibition could apply more widely in breast cancer with E-cadherin loss, in-house siRNA "Achilles' Heel" screen data describing the kinase dependencies in 34 breast tumour cell lines was assessed (Fig 1 H). This identified ROS1 siRNA as selectively targeting the E-cadherin deficient cohort ($p<0.05$, Fig. 1I). Validation experiments confirmed this observation (data not shown), suggesting that the synthetic lethal interaction between ROS1 inhibition and E-cadherin deficiency operated not only in isogenic models, but also in molecularly diverse models of breast cancer, suggesting that this synthetic lethal effect was relatively resistant to the effect of molecular heterogeneity. The sensitivity of the breast tumour cell line models to foretinib or crizotinib and also correlated with E-cadherin protein expression (Fig. 1J,K). By interrogating recently published data describing drug sensitivity effects in *ex vivo* cultured breast cancer explants, crizotinib was also found to be the most significant effect associated with *CDH1* gene copy number loss (data not shown). In investigating the cellular phenotypes associated with these E-cadherin selective effects, E-cadherin defective cells exposed to ROS1 inhibitors exhibited an increase in the proportion of cells with >4N DNA content (Fig. 1L), an increase in the frequency of cells with abnormal mitoses, particularly cells with multiple nuclei, an increase in expression of the G_2/M DNA damage biomarker p21 and an increase in cellular apoptosis as assessed by PARP cleavage and caspase 3/7 activity (data not shown). Live cell microscopy imaging indicated that in response to ROS1 inhibitors, E-cadherin defective cells initiated cytokinesis but failed to complete invagination of the cell membrane at cleavage furrows, resulting in multinuclear cells (Fig 1M). This suggested that the E-cadherin selective effects of ROS1 inhibitors might be explained by abnormal cytokinesis, and the formation of a multinuclear phenotype that could conceivably cause mitotic catastrophe. To assess the *in vivo* therapeutic potential of foretinib and crizotinib, the ability of these drugs to inhibit E-cadherin defective invasive mammary carcinomas derived from *K14cre;Cdh1$^{F/F}$;Trp53$^{F/F}$* (KEP) mice was assessed; these mammary carcinomas show a strong resemblance to human pleomorphic ILCs. In mice that received the drug vehicle alone, tumour growth continued unabated; in contrast, both foretinib or crizotinib treatment had a strong anti-tumour effect on KEP tumour growth and extended the survival of tumour-bearing mice (Fig 1N and data not shown). We also assessed the anti-tumour effect of foretinib treatment in an E-cadherin defective patient-derived breast tumour xenograft (PDX) model, BCM2665, which was derived from a female with ER-negative, HER2-negative, basal-like breast cancer. As before, foretinib significantly inhibited the growth of established tumours ($p<0.0001$ ANOVA) and extended the survival of mice (Fig 1O). These observations were also replicated in subcutaneous xenografts derived from the ER+ ILC cell line MDAMB134VI where mice were treated with crizotinib (data not shown).

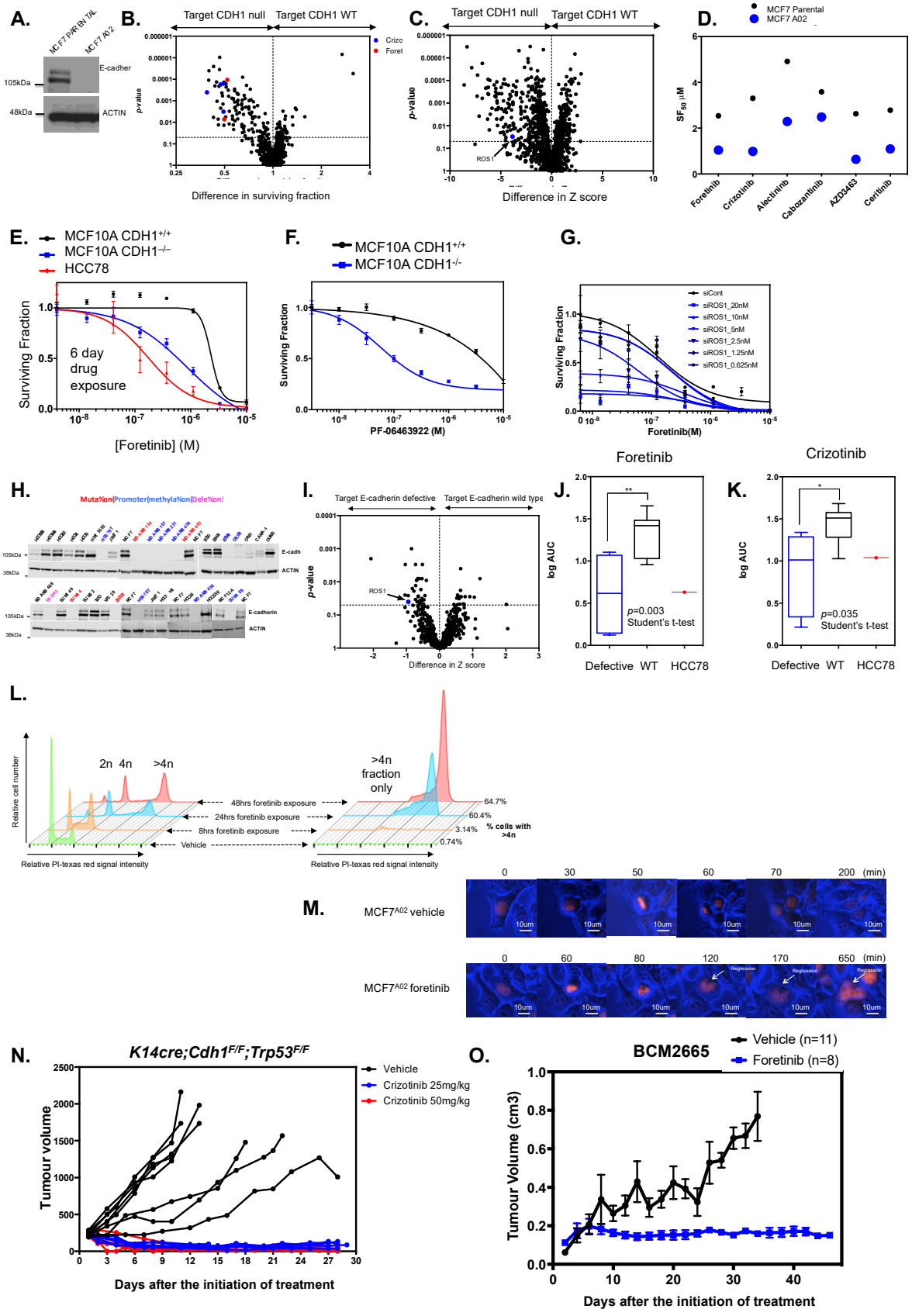


Figure 1. ROS1/E-cadherin synthetic lethality in models of breast cancer

Figure 1 (previous page). *ROS1/E-cadherin synthetic lethality in models of breast cancer*.

A. To identify candidate therapeutic targets for breast cancers with loss of E-cadherin, CRISPR-Cas9 mutagenesis in MCF7 breast tumour cells (ER-positive, luminal A, *PIK3CA* mutant; described hereafter as $MCF7^{Parental}$ cells) was used to generate daughter clones, $MCF7^{A02}$, $MCF7^{B04}$ and $MCF7^{B05}$, with frameshift mutations in *CDH1* and loss of E-cadherin expression ($MCF7^{A02}$and $MCF7^{Parental}$ cells shown in Figure). $MCF7^{A02}$ and $MCF7^{Parental}$ cells were used in two parallel functional screens to identify E-cadherin synthetic lethal effects: (i) a drug sensitivity screen where we assessed the relative sensitivity of cells to an in–house curated library of 80 small-molecule inhibitors that are either in clinical use for the treatment of cancer or in late-stage clinical development and (ii) a parallel siRNA sensitivity screen, using siRNA SMARTpools targeting >1000 cell cycle control genes, kinase-coding genes or DNA repair related genes. **B.** Volcano plot of data from drug sensitivity screens in $MCF7^{parental}$ and $MCF7^{A02}$ cells. The difference in surviving fractions for each small-molecule concentration and *p* values for each $MCF7^{parental}$ vs. $MCF7^{A02}$ comparison are shown. Red and blue dots represent different concentrations of either crizotinib or foretinib identified in the screen as selectively targeting $MCF7^{A02}$ cells. **C.** Volcano plot of data from siRNA SMARTpool sensitivity screens in $MCF7^{parental}$ and $MCF7^{A02}$ cells. Both cell lines were transfected with a siRNA library and cultured for six days. The difference in Z-scores and *p* values for each $MCF7^{parental}$ vs. $MCF7^{A02}$ comparison are shown. Blue dot highlights ROS1 siRNA identified in the screen as selectively targeting $MCF7^{A02}$ cells. **D.** Dot chart illustrating cell survival effects of ROS1/MET/ALK inhibitors in $MCF7^{parental}$ and $MCF7^{A02}$ cells. SF_{50} = surviving fraction 50 (concentration required to cause 50 % reduction in survival). **E, F.** Dose-response survival curves in MCF10A $CDH1^{+/+}$ and MCF10A $CDH1^{-/-}$ cells exposed to foretinib for six days or lorlatinib (PF-06463922). *SLC34A2-ROS1* translocation-positive HCC78 cells are shown as a positive control. **G.** Dose-response survival curves in $MCF7^{A02}$ cells transfected with different concentrations of ROS1 siRNA SMARTpool and subsequently exposed to foretinib for six days. Increasing concentration of ROS1 siRNA caused a dose-dependent reduction in foretinib SF_{50}. **H.** Western blot illustrating E-cadherin expression in 37 breast tumour cell lines (including MCF7 as positive control). Cell line names are colour-coded according to the presence of *CDH1* gene mutations, gene deletion events or *CDH1* promoter hypermethylation events. **I.** Volcano plot of data from the siRNA SMARTpool sensitivity screens in each of the 37 breast tumour cell lines. Blue dot highlights ROS1 siRNA identified in the screen as selectively targeting E-cadherin defective cells. **J.K.** Box whisker plots illustrating foretinib (J) or crizotinib (K) sensitivity in 12 breast tumour cell lines, defined by log_2 area under the curve (AUC) values. Log_2 AUC values for *SLC34A2-ROS1* translocation-positive HCC78 cells are shown as a positive control. **L.** FACS plots illustrating increase in DNA content in E-cadherin defective $MCF7^{A02}$ cells exposed to foretinib, including enlarged image indicating >4n fraction. **M.** Time lapse microscopy images illustrating cell division in E-cadherin defective $MCF7^{A02}$ cells exposed to foretinib. $MCF7^{A02}$ cells were first transfected with a mCherry-H2B plasmid, to facilitate DNA visualization, and then exposed to foretinib for a 24-hour period. Initial formation of the cleavage furrow, followed by formation of a multinuclear cell is highlighted with white arrows. **N.** Therapeutic response to foretinib treatment in mice bearing E-cadherin deficient mammary tumours. Mammary tumour fragments from KEP mice were transplanted into recipient mice; once tumours had established, animals were treated over a 27-day period with either drug vehicle or crizotinib. ANOVA $p<0.0001$ for both foretinib treatment regimes compared to vehicle-treated mice. **O.** Therapeutic response to foretinib treatment in mice bearing BCM2665 PDX. BCM2665 was transplanted into 19 recipient mice; once tumours had established, animals were

treated over a 47-day period with either drug vehicle (n=11), or foretinib (25 mg/kg every other day, n= 8) as shown. ANOVA = p<0.0001.

In addition to these effects in models of breast cancer, the effects of crizotinib in models of gastric cancer have also been assessed. A reanalysis of publically available crizotinib sensitivity data in gastric tumour cell lines indicates that those with reduced E-cadherin expression (defined by *CDH1* mRNA levels) are more sensitive to crizotinib that those with elevated levels of expression (Figure 2).

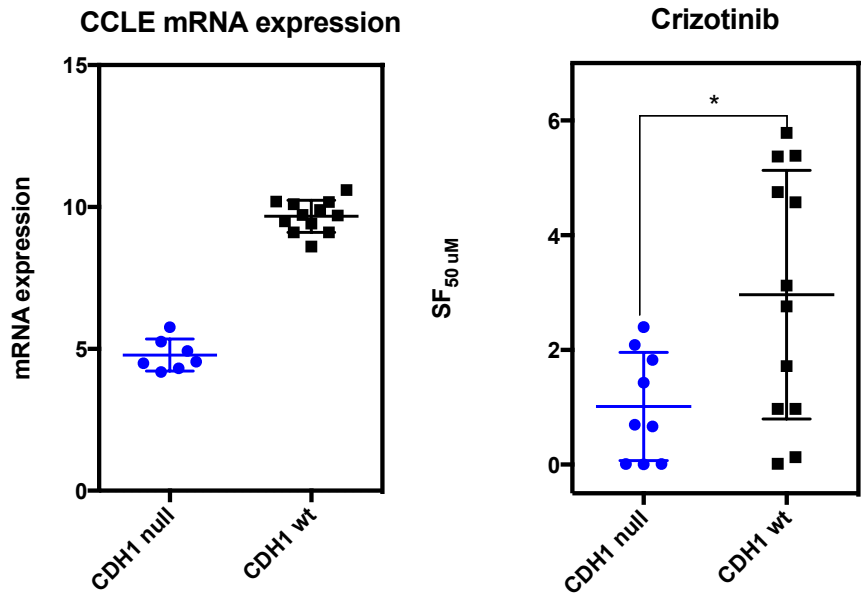


Figure 2. Left: E-cadherin/CDH1 mRNA expression in gastric tumour cell lines profiled as part of the Broad institute Cancer Cell Encyclopedia (CCLE). Tumour cell lines were classified as "CDH1 null" or "CDH1 wild type" based on a threshold of 7 nominal units of expression. Right: Crizotinib sensitivity (as defined by concentration in micromols that causes 50 % inhibition, SF50) in the same gastric tumour cell line panel * p <0.05 Student's t test.

The pre-clinical data described above which underpin the scientific rationale for this study [17]demonstrated that *in vivo* crizotinib sensitivity is also seen in *CDH1* null triple negative breast cancers. A further observation of a response to crizotinib in a triple negative lobular breast cancer organoid established from leptomeningeal cells (Fitzpatrick A. et al., unpublished data) supports this. These patients are excluded from the breast cancer cohort; as such patients would be unsuitable to receive fulvestrant with crizotinib.

Across all anatomic sites, 4% of carcinomas had at least one *CDH1* mutation in a study of 7578 primary carcinomas across 13 anatomic sites. Although breast and gastric cancers were the most common primary tumour sites harbouring *CDH1* mutations, they were also detected in non-melanomatous skin cancers, bladder, colorectal, endometrial, lung, ovarian, prostate and thyroid cancers [20].

Fulvestrant is a selective oestrogen receptor down-regulator (SERD) delivered by intramuscular injection, with efficacy in previously treated ER positive breast cancer including the lobular sub-type [15, 18]. Fulvestrant 500mg is likely the most-efficacious hormone therapy after progression on prior hormonal therapy.

4. TRIAL DESIGN

4.1 Clinical trial objectives and endpoints

4.1.1 Primary objectives and endpoints

Primary objective	Endpoint
To assess confirmed response rate by RECIST 1.1 of crizotinib and fulvestrant in the breast cohort	Confirmed response rate, by RECIST 1.1, of crizotinib and fulvestrant in advanced E-cadherin negative, ER positive lobular breast cancer
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.	Confirmed response rate, by RECIST 1.1, of crizotinib in advanced E-cadherin negative, diffuse gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumours.

4.1.2 Secondary objectives and endpoints

Secondary objectives	Endpoints
To assess the overall safety and tolerability of crizotinib with fulvestrant in the breast cancer cohort and as monotherapy in the gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumour (basket) cohort.	Overall safety and tolerability of crizotinib with Fulvestrant. 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.
To assess the clinical benefit rate (response and stable disease lasting at least 24 weeks) in the breast cancer cohort.	Clinical benefit rate (response or stable disease lasting at least 24 weeks), assessed by RECIST 1.1 by local radiology review.
To assess progression-free survival in each cohort	Progression-free survival, calculated from day 1 of study treatment to the date of radiological disease progression or death from any cause.
To assess overall survival in each cohort	Overall survival, calculated from day 1 of study treatment to the date of death from any cause.

4.1.3 Exploratory objectives and endpoints

Exploratory objectives	Endpoints
To assess the objective response rate in centrally confirmed E-Cadherin negative and *CDH1* mutated tumours	Objective response rate in centrally confirmed E-cadherin negative and *CDH1* mutated tumours

To evaluate candidate predictive biomarkers of sensitivity or resistance to crizotinib in each cohort, including but not limited to tumour Ki67, E-cadherin expression, *CDH1* mutation status, PIK3CA and ESR1 mutations	Objective response rate in patients with *PIK3CA*, *ESR1*, and *CDH1* mutations in baseline plasma DNA
To explore the predictive and/or pharmacodynamic characteristics of peripheral blood and additional tumour tissue biomarkers that may be relevant to the mechanism of action of or resistance to crizotinib	Exploratory assessment of biomarkers of response in baseline tumour biopsy, and of acquired resistance in progression biopsies and plasma DNA.

4.2 Safety Review Committee

To monitor for unexpected adverse effects, we will perform a formal safety review after 3 and 6 patients have received one cycle of treatment (28 days) of crizotinib and fulvestrant in the lobular breast cancer cohort and after 3 and 6 diffuse gastric cancer patients have received one cycle of crizotinib monotherapy (28 days) in the basket cohort.

The SRC will consist of:

- Principal Investigator or delegate from each investigational site
- RM CTU CTC or delegate
- Co-investigators Professor Turner and Dr Starling

4.3 Patient evaluability

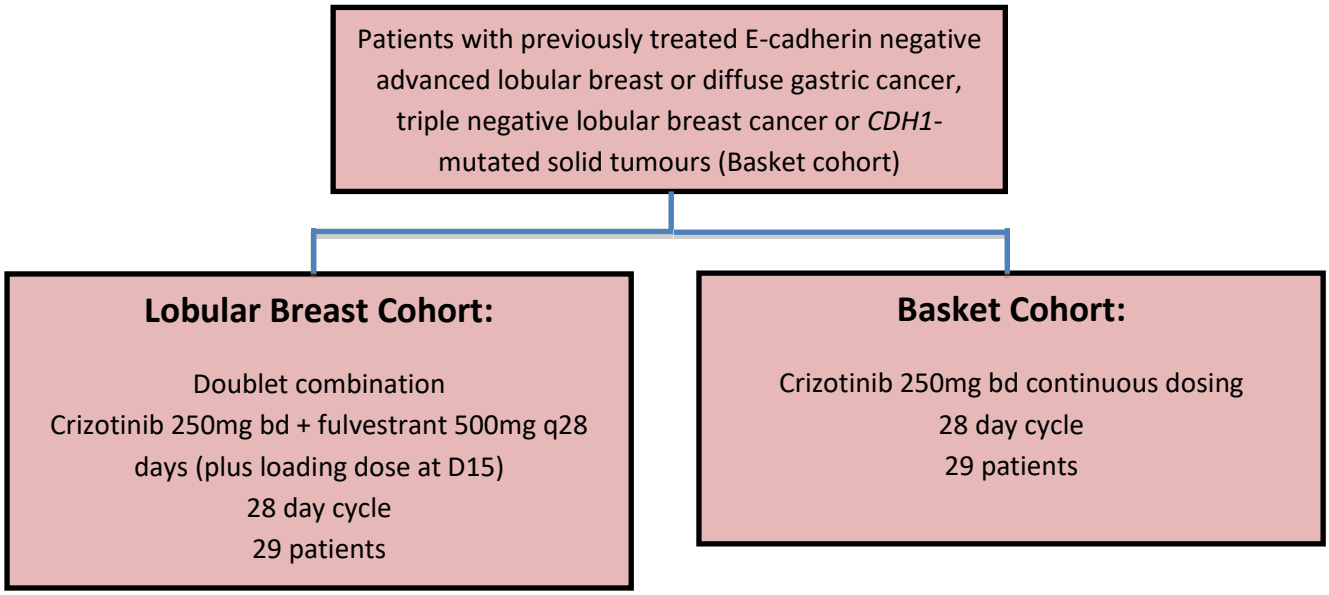
All patients receiving at least one administration of the crizotinib will be considered evaluable for safety and tolerability.

4.4 Design of the clinical trial

This is a phase 2 trial which will investigate the efficacy and tolerability of crizotinib monotherapy in previously treated advanced diffuse gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumour patients and of crizotinib combined with fulvestrant in previously treated lobular breast cancer patients.

The anticipated accrual rate is estimated at 4 patients per month across 8 centres. It is therefore expected that the trial will recruit over 18 months.

Figure 1: Study design



5. PATIENT SELECTION

5.1 Eligibility criteria

The patient must fulfil the eligibility criteria (listed in Sections 4.1.1 and 4.1.2).

5.1.1 Inclusion criteria:

1. Patients with histological diagnosis of E-cadherin negative inoperable or metastatic diffuse gastric cancer (basket cohort),
   Or inoperable or metastatic, E-cadherin negative triple negative lobular breast cancer (basket cohort)
   Or inoperable or metastatic *CDH1*-mutated solid tumour with allele fraction ≥20% (basket cohort)
   Or recurrent inoperable locally advanced E-cadherin negative, ER positive/HER2 negative lobular breast cancer (breast cohort).
   Assessment of E-cadherin, ER and HER2 status as per local assessment.

2. Lobular breast cancer patients previously treated with at least one prior line of therapy including at least one prior line of hormone therapy and a CDK4/6 inhibitor for advanced disease or at least one line of hormone therapy and at least one line of chemotherapy for advanced disease, but no more than three prior lines of chemotherapy for advanced disease.
   Gastric cancer patients previously treated with at least one but no more than three lines of prior therapy for advanced disease OR relapsing within one year of completing (neo) adjuvant chemotherapy OR unsuitable for chemotherapy in the opinion of the investigator (for example patient choice not to have chemotherapy, or no suitable chemotherapy agent).
   Triple negative lobular breast cancer or *CDH1*-mutated solid tumour previously treated with at least one prior therapy for advanced disease, but no more than three prior lines of chemotherapy for advanced disease

3. Measurable disease (RECIST 1.1)

4. Haematological and biochemical indices within the ranges shown below. These measurements must be performed within one week (Day -7 to Day 1) before the patient goes in the trial.

Laboratory Test	**Value required**
Haemoglobin (Hb)	≥ 10.0 g/dL
Absolute neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Serum bilirubin	≤ 1.5 x upper limit of normal (ULN) except for patients with documented Gilberts' disease
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	≤ 2.5 x (ULN) unless raised due to tumour in which case up to 5 x ULN is permissible

Creatinine If creatinine > 1.5 times ULN then: Calculate creatinine clearance (as per standard of care)	≤1.5 times ULN ≥ 50 mL/min (uncorrected value)
Coagulation	INR <1.5 APTT <1.5x ULN

5. Female patients with child-bearing potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial. Both male and female patients of reproductive potential must agree to use two forms of highly effective contraception (see below) for 2 weeks before starting the study treatment, throughout the treatment period and for 90 days after discontinuation of treatment with crizotinib and 2 years after the last dose of fulvestrant.

    - Oral, intravaginal or transdermal combined hormonal contraception
    - Oral, injectable or implantable progesterone-only contraception
    - Intrauterine device
    - Intrauterine hormone-releasing system,
    - Bilateral tubal occlusion
    - Vasectomised partner
    - Sexual abstinence*

    Key: * *it is only considered highly effective if the patient is refraining from sexual intercourse during the entire period of risk associated with the study treatments*

    The oral contraceptive pill may be ineffective when taken with crizotinib so is not an acceptable means of contraception for female patients during this study but can be used by female partners of male patients.

6. 18 years of age or over with written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up.
7. World Health Organisation (WHO) performance status 0,1 or 2
8. Estimated life expectancy of at least 3 months in the opinion of the investigator
9. Pre-/peri-menopausal ER+ lobular breast cancer patients must be willing to receive goserelin injections every 28 days.

    Pre- or peri-menopausal ER+ lobular breast cancer patients may be enrolled if they have ovarian suppression with the LHRH agonist goserelin. Patients must have commenced goserelin or an alternative LHRH agonist at least 4 weeks prior to Cycle 1 Day 1 and continue throughout the study. If a patient has received an alternative LHRH agonist at least 4 weeks prior to study entry, they must switch to goserelin for the duration of the trial.

Post-menopausal female patients, as defined by at least one of the following:

- Age ≥60 years;
- Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause, and serum oestradiol and FSH levels within the institutional laboratory's reference range for post-menopausal females;
- Documented bilateral oophorectomy;
- Medically confirmed ovarian failure.

10. Signed and dated informed consent.

11. Patients willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other procedures.

5.1.2 Exclusion criteria:

1. Systemic chemotherapy or investigational medicinal products during the previous four weeks, or hormonal therapy within 7 days except luteinizing hormone-releasing hormone (LHRH) analogues for ovarian suppression. Bisphosphonates or RANK ligand antagonists are permitted for the management of bone metastases.

2. Previous treatment with any agent that inhibits ROS1

3. Mixed ductal/lobular breast cancer, unless both ductal and lobular components are E-cadherin negative by local assessment

4. Major surgery (excluding minor procedures, e.g. placement of vascular access) within 4 weeks or radiation therapy within 14 days prior to study entry

5. Patients with known symptomatic brain metastases requiring steroids, untreated brain metastases or spinal cord compression

6. Any of the following within 12 months prior to study entry: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, or transient ischemic attack. Uncontrolled hypertension or cardiac dysrhythmia including atrial fibrillation

7. QT interval, corrected >470 ms or the use of bradycardic agents, drugs which prolong the QT interval and/or anti-arrhythmic agents within 5 half-lives before the first dose of crizotinib or during study treatment.

8. Use of drugs that are known potent cytochrome P450 (CYP) 3A4 inhibitors or moderate or strong CYP 3A4 inducers within 12 days before the first dose of crizotinib. Use of CYP3A4 substrates with a narrow therapeutic index (such as ciclosporin) is also not permitted within 12 days prior or during the study treatment.

9. Patients on warfarin. Patients requiring anticoagulation for rate-controlled AF or previous venous thromboembolism should be switched to low-molecular weight heparin.

10. Known HIV or AIDS-related illness, active infection requiring systemic therapy, or positive HBV or HCV test indicating acute or chronic infection

11. Inability or unwillingness to swallow pills, or (for patients receiving fulvestrant) receive IM injections.

12. Other severe acute or chronic medical condition or psychiatric condition, recent or active suicidal ideation or behaviour, or end stage renal disease on haemodialysis, or laboratory abnormality that may increase the risk associated with study participation or investigational products administration or may interfere with the interpretation of results and, in the judgment of the Investigator, would make the patient inappropriate study entry

13. Persisting toxicity related to prior therapy >Grade 1 (except for stable peripheral neuropathy grade ≤2 or alopecia grade ≤2).

14. Pregnancy or lactation.

15. Diagnosis of other malignancy within 5 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or cervix, or low-grade (Gleason ≤6) prostate cancer

16. Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this study. Participation in an observational trial would be acceptable.

17. Immunocompromised status due to current known active infection with HIV or due to the use of immunosuppressive therapies for other conditions

18. Known prior or suspected hypersensitivity to investigational products or to any of the excipients

19. Patients at risk for gastrointestinal perforation (due to e.g., history of diverticulitis).

20. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.

5.2 Patient enrolment

All patients who provide informed consent including any screen failures must be entered onto the patient enrolment log provided to the investigational site.

Before enrolling the patient in the trial, the Investigator or designated representative should confirm the patient is eligible to enter the trial. An enrolment form should be completed prior to enrolment.

To enrol a patient, email the completed enrolment form (see below). A trial number will be allocated. The original enrolment form should be filed within the Investigator Site File.

To enrol a patient please email the completed eligibility and enrolment form to:

ROLo.trial@rmh.nhs.uk (Monday – Friday 09:00-17:00)

6. TREATMENT

6.1 Dosing schedule/treatment schedule

One treatment cycle for crizotinib is 28 days long with continuous dosing of crizotinib 250mg bd po. One treatment cycle for crizotinib + fulvestrant is 28 days long with continuous dosing of crizotinib 250mg bd po and fulvestrant 500mg IM on D1 of each cycle (plus additional D15 loading dose 500mg IM in cycle 1 only).

Patients with documented Gilbert's disease with bilirubin >1.5-≤ 3x ULN should commence crizotinib at a reduced dose of 200mg bd.

6.2 Dose modifications

In the event of significant drug-related toxicity, crizotinib dosing may be interrupted or delayed and/or reduced, as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery followed by dose reduction, if required;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- At start of the new cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Table 1. Common crizotinib toxicities

Common crizotinib toxicities (>10%)	
Haematological:	-Neutropenia (22%) -Anaemia (15%) -Leucopenia (15%)
GI Disorders:	-nausea (57%) -diarrhoea (54%) -Vomiting (51%) -constipation (43%) -Abdominal pain (21%)
General disorders:	-Oedema (49%) -Fatigue (30%)
Cardiac:	-Dizziness (25%) -Bradycardia (12%)
General:	Anorexia (30%)
Eyes:	Vision disorder (62%)
Laboratory:	Raised ALT/AST (32%)
Cutaneous:	Rash (13%)
CNS	-Neuropathy (25%)

	-Dysgeusia (21%)

6.2.1 Dose reductions

6.2.1.1. Dose reduction for crizotinib

Table 2. Management of haematological toxicity (Applies to Anaemia, neutropenia and thrombocytopenia only):

CTCAE grade	Action
Grade 1-2	Continue full dose
Grade 3 (1st occurrence)	Withhold crizotinib until recovers to grade ≤2 then resume at same dose
Grade 4 (1st occurrence) or recurrent grade 3	Withhold crizotinib until recovers to grade ≤2 then resume at 200mg bd
Grade 4 (2nd occurrence)	Permanently discontinue crizotinib

Table 3. Management of non-haematological toxicity:

AE and CTCAE grade	Action
Grade 1-2	Add supportive medications if applicable. Continue full dose
Grade 3-4 ALT or AST with grade 0-1 Bilirubin (1st occurrence)	Withhold crizotinib until recovers to grade ≤1 or baseline then resume at 250mg od. Escalate to 200mg bd if tolerated,
Recurrent grade 3-4 ALT or AST with grade 0-1 Bilirubin **OR** Grade 2-4 ALT or AST with Grade 2-4 Bilirubin	Permanently discontinue crizotinib
Any grade pneumonitis	Withhold whilst pneumonitis investigated with High resolution CT scan. Permanently discontinue crizotinib if diagnosis confirmed.
Grade 3 QTc prolongation	Withhold crizotinib until recovers to grade ≤1, correct electrolytes, then resume at 200mg bd
Grade 4 QTc prolongation	Permanently discontinue crizotinib

Grade 2-3 bradycardia	Withhold crizotinib until recovers to grade ≤1 or HR >60bpm. Evaluate concomitant medications. If causal drug identified and stopped, resume at previous dose once recovers to grade ≤1 or HR >60bpm. If no causal concomitant medication identified/stopped, resume at 250mg od upon recovery to grade ≤1 or HR >60bpm. For Grade 3 bradycardia, monitor pulse daily.
Grade 4 bradycardia	If causal concomitant medication identified/stopped, resume at 250mg od upon recovery to grade ≤1 or HR >60bpm. Monitor pulse daily. If no causal concomitant medication identified/stopped, permanently discontinue crizotinib
Grade 3-4 cardiac failure	Permanently discontinue crizotinib
Grade 4 ocular disorder (visual loss)	Permanently discontinue crizotinib. Ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss, should be performed. Ophthalmological evaluation is recommended if grade 1-3 vision disorder persists or worsens in severity.
Any grade gastric perforation	Permanently discontinue crizotinib
Other grade 1 non-haematological toxicity	Continue crizotinib and fulvestrant
Other grade 2 non-haematological toxicity	Interrupt crizotinib, add supportive medications if indicated (e.g. loperamide, cyclizine) Restart crizotinib at same dose level once resolved to grade 1 or less

Other grade 3 or recurrent grade 2 non-haematological toxicity	Interrupt crizotinib, add supportive medications if indicated (e.g. loperamide, cyclizine) Restart crizotinib at one lower dose level once resolved to grade 1 or less
Other grade 4 or recurrent grade 3 non-haematological toxicity	Permanently discontinue crizotinib

6.2.1.2 Dose reduction for fulvestrant

No dose adjustments to fulvestrant are permitted. Fulvestrant should not be administered to patients with platelets <50x10^9/L

Patients with unacceptable toxicity clearly attributable to fulvestrant may stop fulvestrant and continue with crizotinib monotherapy at the investigator's discretion.

6.2.2 Dose interruptions, delays and re-treatment criteria

Treatment with crizotinib should be interrupted if a patient experiences a Grade ≥3 toxicity or grade 2 toxicity lasting >3 weeks despite appropriate supportive treatment.

Treatment with crizotinib plus/- fulvestrant may be interrupted for a maximum of 28 days until the toxicities have resolved or improved to Grade ≤ 1 and then the drug(s) should be dose-reduced as described in section 6.2.1 *Dose modifications.*

If these toxicities have not resolved or improved to Grade ≤ 1 within this time frame then the patient should be withdrawn from the study.

If despite appropriate dose reductions and or delays, the patient experiences unacceptable toxicities specifically attributed to either crizotinib or fulvestrant, then the patient may continue with single agent treatment without coming off study providing they have completed their first cycle with the combination treatment. The Chief Investigator should be notified if either IMP is discontinued in this way.

Retreatment following interruption for drug related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- Platelet count ≥50,000/mm3
- Neutrophil count: ≥1000/mm3 and no fever
- Grade 3 non-hematologic AEs have recovered to ≤ Grade 1 or baseline.

6.3 Duration of treatment

Treatment should continue until (a) the patient asks to be withdrawn, (b) there is evidence of disease progression or (c) the patient is experiencing unacceptable toxicity or for any of the reasons listed in Section 11.

6.4 Concomitant medication and treatment

Concomitant medication may be given as medically indicated. Details (including doses, frequency, route and start and stop dates) of the concomitant medication given must be recorded in the patient's medical records and the case report form (CRF).

Radiotherapy may be given concomitantly for the control of bone pain, however these irradiated lesions will not be evaluable for response.

The patient must not receive other anti-cancer therapy or investigational drugs while on the trial, other than bisphosphonates or RANK ligand antagonists for the management of metastatic bone disease.

If medically feasible, patients taking regular medication, with the exception of drugs with the potential to prolong QTc and strong inhibitors or inducers of CYP3A4, should be maintained on their regular medications throughout the study period.

6.5 Prohibited medication

The following restrictions will be put in place in the study, **please refer to Appendix 5** of this clinical study protocol for listings of relevant drugs.

Table 4. Prohibited medications

CYP3A inhibitors and CYP3A inducers:
• Potent inhibitors or inducers of CYP3A4 and CYP3A4 substrates with narrow therapeutic indices (including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be avoided **within 2 weeks** before the first dose of study treatment (**3 weeks for St John's Wort and 5 weeks for Phenobarbitone**). • All patients should avoid concomitant herbal supplements and/or ingestion of foods known to potently modulate CYP3A4 enzyme activity from the time they enter the screening period until 2 weeks after the last dose of study treatment.
Anticancer agents:
• Investigational agents and other anticancer agents should not be given while the patient is on study treatment with the exception of hormonal therapy with LHRH analogues for ovarian suppression in pre- or peri-menopausal breast cancer patients.
Radiotherapy:
• Radical Radiotherapy should not be given while the patient is on study treatment.

• Palliative radiation for palliation of symptoms can be given at focal sites i.e. radiation for bony pain but cannot be given to target lesions.
Bradycardic agents, anti-arrhythmics and agents which prolong QTc:
• Avoid using crizotinib in combination with other bradycardic agents, medicinal products that are known to prolong QT interval and/or anti-arrhythmics.

6.6 Permitted medications:

Table 5. Permitted medications

Standard therapies for pre-existing medical conditions	e.g. anti-hypertensives
Bisphosphonates	e.g. pamidronate, zoledronic acid
Receptor activator of nuclear factor kappa-B ligand (RANKL)	e.g. denosumab
Blood or platelet transfusions	
Granulocyte colony stimulating factor [G-CSF] G-CSF is NOT recommended for primary prophylaxis of neutropenia	Therapeutic use for febrile neutropenia in which patients are felt to be at risk of infection related complications (ASCO guidelines) Secondary prophylaxis at the investigator's discretion
Erythropoietin	Already receiving erythropoietin for > 1month at the time of screening Prophylactic erythropoietin should not be started during Cycle 1 of the study but may be started during Cycle 2 and after
Anticoagulation	Subcutaneous heparin is permitted. Patients receiving warfarin should be converted to heparin prior to commencing study treatment.
Palliative radiation	Palliative radiation for palliation of symptoms can be given at focal sites i.e. radiation for bony pain providing there is no evidence of progression

7. PHARMACEUTICAL INFORMATION

7.1 Supply of Investigational Medicinal Products

A complete certificate of analysis and a Qualified Person (QP) certification must be provided with each batch of IMP and be retained in the Investigator Trial File (ITF)/Pharmacy File.

All study drugs will be packaged and labelled in accordance with local regulations and Good Manufacturing Practice, stating that the drug is for clinical trial use only and should be kept out of the reach and sight of children. Crizotinib will be labelled, QP released and distributed by Mawdsleys.

Crizotinib will only be dispatched to sites after receipt of confirmation that the regulatory checklist is complete.

Fulvestrant will not be supplied for this study and must be provided by sites for breast cancer patients enrolled in the study.

For information on all IMP and re-ordering of supplies, contact the RM CTU CTC responsible for the trial who will arrange further supplies.

7.2 Crizotinib

7.2.1 Formulation of Crizotinib

The Drug Product is intended for oral administration.

7.2.2 Storage conditions

The tablets do not require any special storage conditions. All supplies must be stored in a secure, limited access storage area.

7.2.3 Crizotinib administration

Crizotinib will be administered orally twice a day for 28 days for each 28-day cycle.

Patients should be instructed to take their dose at around the same time (no earlier than 1 hour and no later than 4 hours after the scheduled time) each day. If a patient misses a scheduled daily dose, he or she should be instructed to skip that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up.

7.3 Fulvestrant

7.3.1 Formulation of Fulvestrant

Commercially available fulvestrant, 50mg/mL solution should be used. Complete information about fulvestrant formulation can be found in the SPC for Faslodex.

Fulvestrant (Faslodex®) 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. The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlideTM) for connection to the barrel.

7.3.2 Fulvestrant administration

Refer to the SPC for fulvestrant (Faslodex®) for instructions and steps necessary for drug preparation and administration.

Fulvestrant will be administered on Days 1 and 15 during Cycle 1 and then on Day 1 of subsequent cycles thereafter.

Fulvestrant 500mg will be administered intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5mL injections, one in each buttock. Drug preparation and administration will be performed at the site by a physician, registered nurse or other qualified health care provider. Refer to the SPC for Faslodex® for detailed administration instructions.

7.4 Study drug accountability

Accurate records of all IMP shipments, vials dispensed, and all vials returned must be maintained. This inventory record must be available for inspection at any time by the sponsor. IMP supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

The Investigator delegates responsibility for IMP management to the Pharmacist. The Pharmacist undertakes not to destroy any unused IMP unless directed to by the Sponsor. Any unused IMP must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form and also on the IMP Accountability Record. During the course of the trial the Sponsor will check the numbers of tablets of crizotinib shipped to the centre, the number used, and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

8. INVESTIGATIONS SCHEDULE

In cases where a patient has investigations at a different hospital, for example weekly blood samples, then it is the Investigator's responsibility to ensure he/she receives and reviews the results. The results must be recorded on the eCRF and the reports from the other hospitals must be available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

8.1 Pre-treatment evaluations

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records so that the eCRF can be checked against the source data.

Please also refer to the tabulated Schedule of Assessments in Section 8.5.

8.1.1 Obtaining written informed consent

Written informed consent must be obtained from the patient before any protocol-specific procedures are carried out and within four weeks before the patient's first dose of the IMP (crizotinib +/- fulvestrant). Initial discussion and signing of the informed consent must not occur on the same day, as the patient must be given time to think about their commitment to the trial.

Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, and have signed the Study Site Delegation Log, are permitted to gain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8 and 8.3.1.2). The date of the signatures of both the patient and the PI/Sub-Investigator should be the same.

The PI or the Sub-Investigator must inform the patient about the background to, and present knowledge of the normal management of their disease. The PI or the Sub-Investigator must also inform the patient about the IMPs (Crizotinib and fulvestrant *if applicable*). The patient should be aware of the following points:

- The known toxicity of the IMPs and the possibility of experiencing side effects.
- That the IMP combination is new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and he/she has been given information about appropriate medically approved contraception.
- The possibility that crizotinib may impair their fertility, so that fertility preservation measures such as egg or sperm banking can be considered if appropriate.
- That he/she may refuse treatment either before or at any time during the trial and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled.

- Whom to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

Where patients do not have English as a first language and have limited English comprehension; The Sponsor will arrange for the patient information sheet and consent form to be translated into the patient's first language and the site will provide a translator if the investigator is confident this will allow full informed participation in the study. Whenever the consent form is completed the translator should be asked to countersign to state that in their opinion the patient had full understanding and was able to give informed consent. If a telephone translator is used then authorised electronic signature processes at the institution may be used.

A copy of the consent form and patient information sheet must be given to the patient to keep and the original consent form and patient information sheet, must be filed in the Investigator Trial File (ITF) (unless otherwise agreed that the original consent form will be filed in the medical records and the copies kept in the ITF).

8.1.2 Evaluations within four weeks (28 days)

The following must be performed/obtained **within the four weeks before** the patient receives the first dose.

- Written informed consent (as detailed in Section 7.1.1)
- Demographic details
- Medical history including prior diagnosis, prior surgery, prior treatments and any residual toxicities, concomitant diseases, concomitant treatment and allergies
- Tumour biopsy (optional unless no archival recurrent tissue is available)
- Tumour serum markers (CA15-3 and CA125 for breast cancer patients, CA19-9 and CEA for gastrointestinal cancer patients)
- Radiological disease assessments: Radiological measurements (chest, abdominal, pelvis computerised tomography (CT) or magnetic resonance imaging (MRI) scan must be performed within four weeks before the patient receives the first dose. If additional scans of other anatomical sites are performed for accurate baseline assessment i.e. bone scan or MRI brain, then they must also be performed within this timeline. The baseline bone scan can be performed within 6 weeks prior to the first dose of treatment.

Note that all adverse events (AEs), including serious adverse events (SAEs), must be monitored and recorded in the eCRF from the time the patient consents to any protocol-specific procedure.

8.1.3 Evaluations within one week (seven days)

The following must be performed **within one week before** the patient receives the first dose:

- **Pregnancy test:** serum or urine human chorionic gonadotropin (HCG) test to rule out pregnancy at trial entry; results must be obtained and reviewed before the first dose of the IMP is administered if the patient is a woman of childbearing potential.
- **Clinical disease measurements**, if applicable (i.e. patients with clinically assessable disease);
- **Physical examination**: Cardiovascular, respiratory and abdominal examinations plus examination of other systems as clinically indicated.
- WHO performance status evaluation
- Adverse events
- **Vital signs:** Height, weight, body surface area (BSA), WHO performance status, temperature, blood pressure (BP), respiratory rate, pulse oximetry and pulse rate;
- **Collection of plasma for ctDNA**
- **ECG**
- **Laboratory tests** (blood & urine samples) to confirm eligibility.
    - Haematology – haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Coagulation-INR and APTT
    - Biochemistry – sodium, potassium, adjusted calcium, phosphate, magnesium, glucose, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), alanine transferase (ALT) and aspartate aminotransferase (AST).

8.2 Evaluations during the trial

- **Physical examination**: A complete physical examination will be performed within 24 hours before or on Days 1 and 15 of Cycle 1, and on the first day of each cycle subsequent cycle before crizotinib +/- fulvestrant administration.
- WHO performance status (PS) will be repeated during Cycle 1 on (or within 24 hours before) Days 1 and 15 and on the first day of each cycle subsequent cycle before crizotinib +/- fulvestrant administration.
- Bodyweight must be repeated every four weeks, on or within 24 hours before the first day of each cycle.
- Vital signs, temperature, pulse rate, BP, pulse oximetry should be performed as follows:
    - Cycle 1 Day 1 pre-dose

- Prior to dosing on Cycle 1 Day 15
- Day 1 of each subsequent cycle thereafter

- **Adverse events and concomitant treatments**: At each visit, before administration of crizotinib +/- fulvestrant, an assessment of any AE experienced since the previous visit must be made by the Investigator or Research Nurse and the start and stop dates of the AE together with the relationship of the event to treatment with each IMP must be recorded in the medical records. All AEs must be graded according to NCI CTCAE Version 4.0. Any concomitant treatment must also be recorded in the medical records and in the eCRF. (See Section 9 for further details regarding AE reporting requirements.)
- **Laboratory tests**:

  Haematology must be repeated 2-weekly on (or within 72 hours before) Day15 in cycle 1, prior to crizotinib +/- fulvestrant administration. From cycle 2, the frequency of haematology will reduce to Day 1 (+/- 3 days) only.

  Biochemistry must be repeated weekly on (or within 72 hours before) Days 8, 15 and 22 of for the first two cycles. From cycle 3, the frequency will reduce to Day 1 only (+/- 3 days).

  NB. Haematology and biochemistry may be performed up to 3 days before dosing in any cycle.

  - Haematology – haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
  - **Day 1 of each cycle (from cycle 2 onwards)** Biochemistry & pregnancy test (pre-menopausal females only). – sodium, potassium, adjusted calcium, phosphate, magnesium, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), alanine transferase (ALT) and aspartate aminotransferase (AST).
  - **Day 8, 15 and 22 during cycles 1 & 2 only** Biochemistry – sodium, potassium, adjusted calcium, phosphate, magnesium, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), alanine transferase (ALT) and aspartate aminotransferase (AST) and glucose.

- NB. As described in section 16.9 for crisis situations, biochemistry may be performed locally at the C1D8, C1D22, C2D8, C2D15 and C2D22 timepoints.

- **ECG:** A resting ECG will be performed on day 1 of each cycle, except for cycle 1, for which it must have been performed within 7 days prior to D1.
- **Tumour serum markers (if applicable):** must be repeated prior to day 1 of every cycle (4 weeks).
- **Radiological assessment of disease:** CT or MRI TAP must be repeated every 8 weeks of crizotinib +/- fulvestrant, with the first assessment scheduled on cycle 3 day 1 (+/- 3 days). After the 24 week scan the frequency of imaging may be reduced to every 12 weeks at the Investigator's discretion. Other investigations such as MRI brain or bone scan to be performed only if clinically indicated.

- **Collection of blood sample for circulating tumour DNA** (**Parts 1 and 2** will be collected on day1 pre-dose on all cycles and prior to D15 in cycle 1 only. A further sample is required at disease progression.
- **Tumour biopsy (optional):** This will be performed at D15 of cycle 1 and after disease progression is confirmed radiologically in consenting patients.
- Any patients within the breast cohort who are not receiving a bisphosphonate or denosumab should be assessed at least annually for osteoporosis as per routine clinical practice.

8.2.1 Evaluations when disease progression is confirmed

If disease progression is confirmed clinically or radiologically, the following evaluations should be performed within 7 days:

- Adverse events
- Concomitant medications
- Performance status
- Collection of blood for ctDNA
- Optional tumour biopsy in patients who have consented to this.

8.3 Evaluations at 'off-study' visit

Evaluations at the 'off-study' visit must be performed 28+/-3 days after the last dose of crizotinib. The following investigations must be done:

- a symptom-directed physical examination including WHO performance status, temperature, pulse rate, BP, bodyweight, BSA.
- haematology tests: FBC
- biochemistry tests: U&E, LFT, Calcium, CA15-3 and CA125 (breast cohort or basket cohort triple negative lobular breast patients) or CEA and CA19-9 (basket cohort gastrointestinal cancer patients), pregnancy test (pre-menopausal females only)
- ECG
- assessment of tumour disease with CT or MRI TAP, unless assessment has been performed within the previous four weeks (28 days);
- assessment of AEs
- assessment of concomitant treatments.
- Optional tumour biopsy and collection of blood sample for circulating tumour DNA. These should ideally be performed within 7 days of progression being identified.

8.4 Follow-up

Patients will be followed up for safety for 28 days after the last administration of crizotinib. If any AEs and SAEs are considered to have a highly probable, probable or possible causal relationship to crizotinib or fulvestrant, and are still present at 28 days after the last administration then the patient will be followed up monthly afterwards until resolution, to baseline or stabilisation of these events, unless the patient starts another anti-cancer treatment.

Patients who stop study treatment for reasons other than disease progression will be followed-up for progression events with ongoing CT scans every 8 weeks, unless they withdraw their consent to this imaging follow-up.

Patients will also be followed-up for survival every 6 months, usually by telephone, unless they withdraw consent to the study.

8.5 Table 6: Schedule of events (Refer to sections 8.1.2-8.4 for details)

	Screening (within 28 days before first dose)	Screening (within 7 days before first dose)	Day 1 +/- 1 day	Day 8 +/- 1 day	Day 15 +/- 1 day	Day 22 +/- 1 day	Day 29 (Cycle 2 D1) +/- 3 days	Cycle 2 Day 8 +/- 3 days	Cycle 2 Day 15 +/- 3 days	Cycle 2 Day 22 +/- 3 days	Cycle 3 Day 1 +/- 3 days	Cycle 4 Day 1 +/- 3 days	Day 1 of each cycle +/- 3 days	Day 28 after last dose +/- 3 days	Follow up (Every 8[(d)] weeks until progression) +/- 3 days	At disease progression +/- 7 days	Survival Follow Up (every 6 months)
Archival tumour tissue available	x																
CT or MRI TAP (or PET/CT)	x										x			x	x		
Bone scan[(a)]	x																
MRI brain[(b)]	x																
Tumour biopsy	x[(c)]				x*											x*	
Pregnancy test (if pre-menopausal)		x					x				x	x	x	x			
ECG		x					x				x	x	x	x			
FBC		x			x		x				x	x	x	x			
Coagulation		x															
U&E, LFT, Ca2+		x		x	x	x	x	x	x	x	x	x	x	x			
CA15-3 and CA125 (Breast patients) CEA and CA19-9 (gastrointestinal cancer patients)	x						x				x	x	x	x			

Circulating tumour DNA		x			x		x				x	x	x			x	
BP, Pulse, Temp, O_2 sats,		x	x		x		x				x	x	x	x			
Body weight		x			x		x				x	x	x	x			
Physical examination		x	x		x		X				x	x	x	x			
Informed consent	x																
Oncological history, demographics and co-morbidities	x																
Check AEs		x	x		x		x				x	x	x	x		x	
Check con-meds	x		x		x		x				x	x	x	x		x	
WHO PS		x	x		x		x				x	x	x	x		x	
Check crizotinib compliance					x		x				x	x	x				
Fulvestrant injections (breast cohort only)			x		x		x				x	x	x				
Survival FU																	x

*optional

a) For patients with known bone metastases a bone scan should be performed at baseline (within 6 weeks prior to first dose) then as clinically indicated
b) Only required for patients with known CNS metastases or symptoms/signs suggestive of new brain metastases
c) Optional unless no archival recurrent tissue biopsy is available
d) Frequency may be reduced to *every 12 weeks after cycle 6* at the investigator's discretion

9. PHARMACODYNAMIC ASSESSMENTS

9.1 Predictive biomarker assays

9.1.1 Analysis of tumour biopsy material for predictive biomarker analysis

DNA extracted from archival or fresh tumour material (in those patients who consent to the optional tumour biopsies section 8.2.1) will be analysed for somatic mutations, which may represent putative predictive biomarkers. If possible, tumour biopsies will be undertaken at disease progression for analysis of putative biomarkers of resistance.

Archival tumour material will be collected for all patients enrolled into the study. The tumour samples will preferably be in the form of a formalin fixed paraffin embedded block of tissue derived from a metastatic site (or the primary tumour for patients presenting with *de novo* metastatic disease). If this is not possible, 10-20 slides of freshly prepared unstained 5 micron sections from the archival tumour block may be provided. Analysis may be done retrospectively for patients.

Core needle biopsies will be collected according to the institutional procedure and divided into 2 samples, one to be snap frozen and one to be formalin fixed and embedded in paraffin (FFPE) as per local procedures for predictive biomarker analysis.

Tumour biopsies will be analysed at the laboratories of the Institute of Cancer Research. Please refer to the Study Laboratory Manual for handling, storage and shipment of samples.

9.1.2 Collection of plasma samples for circulating free DNA

Blood sample 20mls in EDTA/Streck tubes for the analysis of circulating tumor DNA (ctDNA) will be taken and processed according to the lab manual. Samples will be analyzed in Professor Turner's laboratory at the Institute for Cancer Research to identify somatic mutations, which may represent putative predictive biomarkers. This will be correlated with mutations detected in submitted tumour specimens.

The plasma samples should be taken at

- Prior to drug dosing: at screening Day -28 to Day-1 of Cycle 1
- Cycle 2 onwards on Day 1
- Off Study: ≤ 28 days after last dose of IMP, on progression

10. ASSESSMENT OF SAFETY

10.1 Adverse event definitions

10.1.1 Adverse event

Follow-up of AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient starts another anti-cancer therapy.

An AE is any untoward, undesired or unplanned occurrence in a patient administered an IMP. An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.

Other reportable events that must be treated as AEs are listed below:

- Pregnancy exposure to the IMP. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of the last IMP administration must be reported to the Sponsor in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Any AE associated with an overdose or incorrect administration of IMP. An overdose or incorrect administration of IMP is not an AE unless it results in untoward medical effects.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial, including relevant abnormal laboratory values. Abnormal laboratory values deemed clinically significant by an investigator should be reported as adverse events. Grade 3-4 neutropenia, any grade reduction in albumin and ALT/AST or creatinine elevation grade 1 or more should be reported as an AE.

10.1.2 Adverse reaction (AR)

All untoward and unintended responses to the study drug related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions, i.e. an AR is possibly, probably or definitely related to the study drug. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

10.1.3 Serious adverse events (SAEs)

An SAE is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – see Section 10.3.3);
- results in persistent or significant incapacity or disability;
- is a congenital anomaly or birth defect;
- is any other medically important event.*

* A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent an SAE. It should be noted that medically important events might be identified before or at any point in the study.

10.1. 4 Serious Adverse Reaction (SAR)

An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

10.1.5 Suspected, unexpected, serious, adverse reactions (SUSARs)

A SUSAR is a serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:

- in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product
- in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

10.2 Operational definitions for (S)AEs

For eligible patients, SAE and adverse event (AE) collection and monitoring commences from the time the patient gives their written consent to participate in the trial and continues for 28 days after the last administration of crizotinib or fulvestrant (investigational medicinal product [IMP]).

All AEs will be graded according to CTCAE version 4, recorded in the patient's medical records and captured in the CRF.

10.2.1 Assessment of Severity

Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in section 10.3.

10.2.2 Assessment of Seriousness

The seriousness of an adverse event is assessed using the criteria outlined in section 10.1.3.

In addition, for all crizotinib-treated patients, Grade ≥2 PSTE (except for Visual field defect, for which Grade ≥3 is the standard) or SVL should be treated as Serious Adverse Events, regardless of relatedness to study drug. Please refer to **APPENDIX 6**.

10.2.3 Determining adverse event causality

The relationship of an AE to the IMP is determined as follows.

Highly probable • Starts within a time related to the IMP administration and • No obvious alternative medical explanation.
Probable • Starts within a time related to the IMP administration and • Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible • Starts within a time related to the IMP administration and • A causal relationship between the IMP and the AE is at least a reasonable possibility.
Unlikely • The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.
Not related • The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc.) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

10.2.4 Expectedness

An assessment of expectedness will be made by the Chief Investigator (or delegate) against section 4.8 of the current versions of the crizotinib or fulvestrant SmPC.

10.3 Recording and reporting of Serious Adverse Events (SAEs) / Serious Adverse Reactions (SARs)

10.3.1 Reporting of Serious Adverse Events (SAEs) / Serious Adverse Reactions (SARs)

All SAEs / SARs occurring from the time of written informed consent until 28 days post cessation of trial treatment must be recorded on the SAE Report Form and emailed to ROLo.trial@rmh.nhs.uk or faxed to 0208 915 6762 to RM CTU **within 24 hours** of the site staff becoming aware of the event.

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4.0 must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Sponsor on a new SAE report form.

RM-CTU will inform the sponsor/CI and Pfizer about the event and once all resulting queries have been resolved, the SAE report form will be retained in the site file.

For each **SAE / SARs,** the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- Whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to RM CTU at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Should the Investigator become aware of any drug-related SAEs after the patient goes 'off study', these must also be reported to the Sponsor within the specified timelines above.

10.3.2 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SUSARs (as defined in section 10.1.5) are subject to expedited reporting. The Sponsor delegates the responsibility of SUSAR notification to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the Sponsor, MHRA and REC. The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

10.3.2.1 Fatal or life-threatening SUSARs

All parties listed in 10.3.2 must be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

10.3.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 9.3.2 as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

10.3.2.3 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

a) A suspected investigational medicinal product,
b) An identifiable subject (e.g. trial subject code number),
c) An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) An identifiable reporting source,

And, when available and applicable:

a) A unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
b) A unique case identification (i.e. sponsor's case identification number).

10.3.2.4 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

10.3.2.5 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

10.3.3 Events exempt from being reported as SAEs

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the case report form (CRF).

Screening period – SAEs occurring in the period prior to administration of crizotinib +/-fulvestrant from the time of informed consent to the day prior to cycle 1 day 1 are exempt from reporting if they are not related to the design or conduct of the trial.

Elective admissions – Elective admissions to hospital for procedures which were planned and documented in the medical records at the time of consent are not SAEs, and do not require SAE reporting.

Hospitalisation associated with disease progression does not require SAE reporting, but associated AEs should be fully documented in the CRF.

10.4 Recording of adverse events and serious adverse events in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The Safety Review Committee and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

10.5 Follow-up of adverse events

Follow-up will continue until all the necessary safety data for the event has been gathered and until the AE or SAE has resolved, returned to baseline or stabilised. The Sponsor will make requests for further information to the trial site at regular intervals. Requested follow-up information should be reported to the Sponsor in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information should be reported as soon as possible.

Any SUSAR related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

10.6 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

- **Email: ROLo.trial@rmh.nhs.uk** or
- **Telephone: 0208 915 6506**; or
- **Fax: 0208 915 6762**

The notification must include:

- the date of the USM;
- who took the decision; and
- Why action was taken.

The Sponsor will then notify the MHRA and the relevant REC immediately and in any event no later than three days of USM initiation, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures. The initial notification to the MHRA and REC should be by telephone. A notice in writing must be sent within 3 days. The notice should set out the reasons for the USM and the plan for further action.

10.7 Pregnancy

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for 90 days afterwards (basket cohort), 2 years after (breast cohort). This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved highly effective methods contraception should be used, such as:

- oral contraceptives and an intra-uterine device (IUD)
- intra-uterine device (IUD) and your partner has had a vasectomy or you have had bilateral tubal occlusion

Female patients with child-bearing potential must have a negative urine or serum pregnancy test within 7 days prior to start of trial. Both male and female patients of reproductive potential must agree to use two forms of highly effective contraception (see below) for 2 weeks before starting the study treatment, throughout the treatment period and for 90 days after discontinuation of treatment with crizotinib and 2 years after the last dose of fulvestrant.

- Oral, intra-vaginal or transdermal combined hormonal contraception
- Oral, injectable or implantable progesterone-only contraception
- Intrauterine device
- Intrauterine hormone-releasing system,
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence*

*Key: *it is only considered highly effective if the patient is refraining from sexual intercourse during the entire period of risk associated with the study treatments*

The oral contraceptive pill may be ineffective when taken with crizotinib so is not an acceptable means of contraception for female patients during this study but can be used by female partners of male patients

It should be explained to the patient that if his partner is pregnant or breast-feeding when he enters the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to the crizotinib+/-fulvestrant.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within 90 days of last crizotinib administration or 6 months of last fulvestrant administration (breast cohort) must be reported to the Sponsor within 24 hours of the site staff becoming aware of it using a Pregnancy Notification Form.

In addition, due to the effect of crizotinib on oral contraception, all pregnancies should be treated as adverse events, as per section 10.1.1.

It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. The Sponsor will follow-up all pregnancies for the pregnancy outcome via the Investigator and document on the pregnancy form.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to six months after the last IMP administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient and the baby should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this.

11. ASSESSMENT OF EFFICACY

11.1 Measurement of disease

Disease must be measured according to the RECIST criteria (version1.1) given in Appendix 3.

11.2 Timing and type of tumour assessments

A thorough clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the investigational medicinal product (IMP). The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

All radiological assessments must be performed within four weeks before starting treatment. The interval between the last anti-cancer therapy and these measurements must be at least four weeks (28 days). All clinical measurements to assess response must be done within **one** week before the patient starting treatment.

All complete (CR) and partial responses (PR) must be confirmed by two consecutive observations not less than four weeks apart.

Copies of the scans must be available for external independent review if requested by the Sponsor.

11.2.1 Baseline evaluations

These must include radiological measurements and as indicated chest, abdominal and pelvic computerised tomography (CT) scans, magnetic resonance imaging (MRI), bone scan and/or clinical measurements as appropriate. All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is strongly recommended, as this aids external independent review of responses. (See Section 1.2.1 of RECIST 1.1 criteria)

11.2.2 Evaluations during and at 'off-study'

Tumour assessments must be repeated every 2 cycle(s)/8 weeks if continuous treatment or more frequently, when clinically indicated. All lesions measured at baseline must be measured at every subsequent disease assessment and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent.

All patients, who are removed from the trial for reasons other than progressive disease, must be re-evaluated at the time of treatment discontinuation (+/- 28 days), unless a tumour assessment was performed within the previous four weeks.

It is the responsibility of the Principal Investigator to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST 1.1 criteria.

11.3 Tumour response

All patients who meet the eligibility criteria will receive at least two cycles of trial medication and have a baseline assessment of disease will be evaluable for response by RECIST criteria. To be assigned a status of complete response (CR) or partial response (PR), changes in tumour measurements must be confirmed by repeat measurements performed no less than four weeks after the response criteria are met. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of the investigational medicinal products (IMP) crizotinib +/- fulvestrant are given.

Should rapid tumour progression occur before the completion of 4 weeks the patient will be classified as having early progression (EP).

Tumour response should be classified as “not evaluable” (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Expert reviewers appointed by Sponsor may undertake an independent review of all the Investigator’s assessed objective responses (CR and PR). The expert reviewers will include at least one specialist who is not an Investigator in the trial. In case of disagreement between the Investigator’s and the expert reviewers’ assessment, discussion will take place between the two parties in order to reach a consensus. However, if it is not forthcoming, the assessment of the expert reviewers will be retained in the clinical study report. The eCRF will reflect the Investigator’s opinion and the primary analysis of response will be based upon local assessment of response.

11.3.1 Recording of response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF, even though the criteria for determination of CR or PR by the protocol must be confirmed after two consecutive observations, no less than four weeks apart.

12. DISCONTINUATION OF TREATMENT/WITHDRAWAL FROM TRIAL

The Investigator must make every reasonable effort to keep each patient on trial for the whole duration of the trial (i.e. until 28 days after last combination therapy administration). However, if the Investigator removes a patient from the trial or if the patient declines further participation, final 'off-study' assessments should be performed before any therapeutic intervention. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the trial, must be recorded in the medical records and in the eCRF.

Patients who are removed from the trial due to adverse events (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the serious adverse event (SAE) report form where necessary.

The following are justifiable reasons for the Investigator to withdraw a patient from trial.

- Unacceptable toxicity
- AE/SAE
- Withdrawal of consent
- Serious violation of the trial protocol (including persistent patient attendance failure and persistent non-compliance)
- Sponsor's decision to terminate the trial
- Withdrawal by the Investigator for clinical reasons not related to the IMP
- Evidence of disease progression
- Symptomatic deterioration

Patients that are discontinued from the study are still evaluable as defined in section 14.1

13. DEFINING THE END OF TRIAL

The 'end of trial' is defined as the date when the last patient has completed the 'off-study' visit or the final follow-up visit (whichever is the latter).

It is the responsibility of the Sponsor to inform the Medicines and Healthcare products Regulations Agency (MHRA) and the Main Research Ethics Committee (REC) within 90 days of the 'end of the trial' that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the Sponsor, the Sponsor will notify the MHRA and the Main REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

The entire trial will be stopped when:

- The drug is considered too toxic to continue treatment before the required number of patients being recruited.
- The stated number of patients to be recruited is reached.
- The stated objectives of the trial are achieved.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the trial, Sponsor and the Investigators must ensure that adequate consideration is given to the protection of the patient's interest.

14. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

An interim analysis will be conducted after the first 10 patients in the first stage of each cohort have been recruited and treated and have at least reached their 1st scan.

The final analysis will be conducted after one of the following conditions is met.

- The trial is terminated early (for example, due to toxicity).
- All patients have had the opportunity to receive 1 cycle of treatment and have completed their 'off-study' visit (i.e. 28 days after the last dose of crizotinib +/- fulvestrant).

Once one of the conditions is met, a data cut-off date will be established. All patient visits occurring on or before this date will be analysed and summarised in the final clinical study report. Any data collected after this date will be summarised in a supplemental report.

14.1 Statistical Analysis

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the trial conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol violations, IMP accountability and other data that impact on the general conduct of the trial.

Baseline characteristics will be summarised for all enrolled patients.

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

The statistical analysis below will be performed in each cohort separately.

<u>Primary Endpoint</u>

Response rate will be described as a proportion of patients with a best overall response of CR or PR with the 95% CI. Patients who stop study treatment before the first response evaluation scan has been performed with clinical progression will be treated as disease progression.

<u>Secondary Endpoints</u>

Toxicities will be presented as frequencies and proportions for each cohort separately.

Clinical benefit rate will be presented as the proportion of patients with a best over response of CR, PR or SD maintained for a minimum of 6 months, with the 95% CI.

Progression free survival will be calculated using Kaplan Meier methods. This will be defined from the date 1 of study treatment to date of radiological disease progression or death from any cause. Any progression free surviving patients will be censored at last follow up.

Overall survival will be calculated using Kaplan Meier methods. This will be defined from the date 1 of study treatment to date of death from any cause. Any patients who are alive or lost to follow-up will be censored at last follow up.

Exploratory Endpoints

The objective response rate in each cohort will be presented in patients with centralised confirmed E-cadherin negative and *CDH1* mutated tumours. The objective response rate will also be presented in patients with *PIK3CA*, *ESR1* and *CDH1* mutations and other biomarkers. These will be presented with 95% CIs.

14.1.1 Subject Replacement Strategy

Patients who have died or withdrew before treatment started or did not complete the required safety observations will be replaced. Patients who stop the study treatment prior to response evaluation for reasons other than progression (patient choice or toxicity) will also be replaced.

14.2 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. Laboratory variables will be described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Adverse events (AEs) will be reported for each dose level and presented as tables of frequency of AEs by body system and by worse severity grade observed. Tables should indicate related and unrelated events. Laboratory data will be presented by cohort at each observation time. Values outside normal limits will be identified and summarised by frequency distribution.

14.3 Pharmacodynamics

Archival tumour and/or baseline fresh tumour biopsy will be tested centrally for E-cadherin by immunohistochemistry and subjected to sequencing using next generation sequencing (NGS). RNA will be extracted for gene expression studies. These studies will be repeated on the end of tumour biopsy and baseline and end of treatment plasma DNA.

Mutations detected on the baseline biopsy/plasma DNA sample will be tracked on subsequent plasma DNA samples and correlated with treatment response.

Objective response rate will be calculated in patients with centrally confirmed E-cadherin negative and *CDH1* mutated baseline tumours and patients with *PIK3CA, ESR1*, and *CDH1* mutations or *MET* amplification in baseline plasma DNA. There will be no formal statistical analysis of this exploratory endpoint.

14.4 Anti-tumour activity

Documenting anti-tumour activity is the primary objective of this trial. Patients must receive at least one cycle of the trial medication to be evaluable for response. Objective responses as defined by RECIST 1.1, the best tumour response achieved by each patient while on trial and the progression free survival, and duration of response will be presented in the data listings. Clinical benefit rate will be defined as the proportion of patients with a partial or complete response or stable disease lasting at least 24 weeks.

14.5 Sample size considerations

Optimal Simon 2 stage design for each cohort.

Breast cancer cohort: Fulvestrant alone is anticipated to have a response rate (RR) of 5% in the population studied, due the extent of prior pre-treatment. Therefore 29 patients are required to exclude a RR of 5% and detect a 20% RR (p0=0.05, p1=0.2, power 80%, alpha 0.05). A single response in the first 10 evaluable patients is required to proceed to the second stage. Four patients with tumour response among the total of 29 evaluable patients in both stages are required to reject the null hypothesis.

Gastric cancer, triple negative lobular breast cancer or *CDH1*-mutated solid tumour (basket) cohort: In this cohort, 29 patients are required to exclude a RR of 5% and detect a 20% RR (p0=0.05, p1=0.2, power 80%, alpha 0.05). A single response in the first 10 evaluable patients is required to proceed to the second stage. Four patients with tumour response among the total of 29 evaluable patients in both stages are required to reject the null hypothesis.

15. TRIAL COMMITTEES

15.1 Trial management group

The Trial Management Group (TMG) comprises the Chief Investigator, other co-investigators, the study statistician and RM CTU CTC. The TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference 3-6 monthly and in person as needed. The Trial Management Group will also act as the safety review committee and has an independent chair. The role of the committee is to review the safety of the first 3 and 6 breast cohort patients to receive one cycle of the treatment combination of fulvestrant with crizotinib and to also review safety of the first 3 and 6 basket cohort patients to have received one cycle of crizotinib monotherapy.

15.2 Independent Data Monitoring Committee

Reports to the IDMC will be produced by the statistician. The data monitoring committee will be informed in writing of the safety review committee's assessment of toxicity for the first 3 and 6 lobular breast cancer patients receiving one cycle of crizotinib and fulvestrant and the first 3 and 6 basket cohort patients receiving 1 cycle of crizotinib monotherapy.

The IDMC will meet after the first stage where 10 patients have been recruited and have at least 1 scan. The IDMC will consider data in accordance with the statistical analysis plan and will be advisory to the TSC.

15.3 Trial Steering Committee

A Trial Steering Committee (TSC) will provide overall supervision for the ROLo Trial. The ultimate decision for the continuation of the trial lies with the TSC.

16. ADMINISTRATION

This trial is conducted under a clinical trial authorisation (CTA) and approval from the Medicines and Healthcare products Regulations Agency (MHRA) and the relevant Research Ethics Committee(s) will be obtained before the start of this trial. This trial is sponsored by The Royal Marsden NHS Foundation Trust (RM). Applicable regulatory requirements are described in this section.

16.1 Protocol deviations and amendments

Do not deviate from the protocol unless approval has been obtained from the Sponsor.

Eligibility waivers are strictly prohibited.

Amendments to the protocol may only be made with the approval of the Sponsor, CI and statistician. A protocol amendment will be subject to review by the sponsor. Ethics Committee favourable opinion (and MHRA approval if appropriate) will be obtained by the RM CTU CTC on behalf of the CI before the amendment can be implemented and incorporated into the protocol if necessary.

16.2 Completion of the case report form (CRF)

Electronic CRFs (eCRFs) will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have signed the Study Team Responsibilities Signature Log/Delegation Log provided by the RM CTU and have been authorised by the Investigator should enter or change data in the eCRFs. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference.

Data will be entered directly into eCRFs by authorised site personnel.

Once data has been entered by the site personnel on the eCRF, the data will be reviewed and checked for error and inconsistencies by the RM CTU CTC.

Once the patient is 'off study' and the eCRF has been fully completed, the Investigator must provide an electronic sign-off to authorise the complete subject casebook.

16.3 Trial performance and monitoring

16.3.1 Management of the study

The RM CTU Clinical Trials Coordinator will be responsible for the day-to-day coordination and management of the trial. The RM Clinical Trials Unit will act as custodian of the data on behalf of the sponsor. The RM CTU is responsible for all duties relating to pharmacovigilance in accordance with section 9.

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. The Sponsor must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the RM CTU is responsible for monitoring data quality in accordance with Royal Marsden Hospital's standard operating procedures (SOPs). Before the trial start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the Clinical Coordinator to:

- review trial records and compare them with source documents;
- check pharmacodynamics samples and storage;
- discuss the conduct of the trial and the emerging problems with the Investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the available facilities remain acceptable.

All unused drug supplied must be returned to the supplier, or if authorised by Sponsor properly destroyed at the Investigator site by an authorised person who will provide signed confirmation.

It is the responsibility of the Sponsor to inform the Main REC within 90 days of the 'end of the trial' (i.e. last patient study visit) that the trial has closed.

16.3.2 Source document verification

Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

All data collected in the eCRF must be verifiable by the source data. Therefore, it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CTM direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be documented on the source data verification (SDV) form and the monitoring report.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor appointed to audit the trial, and by regulatory authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

16.4 Clinical study report

All clinical data will be presented at the end of the trial on final data listings. The CI, RM CTU CTC and RM statistician will prepare a clinical study report based on the final data listings. The report will be submitted to the Investigator(s) for review and confirmation it accurately represents the data collected during the course of the trial. A summary of the final clinical report will be provided by the Sponsor to the MHRA and to the Research Ethics Committee.

16.5 Record retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (including those detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans, trial related documents and copies of the eCRFs, associated audit trail and serious adverse event (SAE) report forms, shall show whether the Investigator has complied with the principles and guidelines of Good Clinical Practice (GCP).

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for 5 years. Records must not be destroyed without prior written approval from the Sponsor.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

16.6 Ethical considerations

Before starting the trial, the protocol, patient information sheet and consent form must be approved by the ICR/RM joint Committee for Clinical Research and the appropriate Ethics Committee.

The confidentiality of patients participating in this trial will be protected and each participant will be assigned a unique trial number at the point of registration which will be used to identify eCRFs and anything else sent to the sponsor or other third parties. No patient identifiable data will be shared outside of the participating site.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor and Chief/Principal Investigator must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended).

16.7 Indemnity

This trial is being carried out under the auspices of The Royal Marsden NHS Foundation Trust.

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements for clinical negligence.

16.8 Publication policy and press releases

The trial results will be submitted for publication in a relevant medical journal with authorship according to the criteria defined by the ICMJE (http://www.icmje.org). These state that: Authorship credit should be based 1) substantial contributions to conception and design, acquisition of data, or

analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Draft publications (manuscripts, abstracts, slides and posters) should be submitted to the RM CTU Clinical Trial Coordinator for circulation to the relevant parties and the statistician to allow sufficient time for review prior to submission.

The Sponsor shall receive copies of abstracts, slides, posters and manuscripts for review in advance of submission.

The results of the breast and basket cohorts may be presented and published separately or combined.

Following publication, the sponsor will produce a lay summary of the results to be published on the Royal Marsden's website or upon request to be distributed to study participants.

16.9 Off-site study procedures in case of crisis situation

In cases of emergencies including, but not limited to viral pandemics, natural disasters or war, to continue patient safety and minimise risks to the study integrity, certain study procedures may be conducted remotely for patients included in the study. Any such changes will be temporary and based upon a risk assessment specific to the crisis and the MHRA and Ethics committee will be informed as required.

Temporary study changes will include:

1. Study visits conducted by telephone
2. Laboratory testing performed at the patient's local hospital or GP surgery
3. Study drug shipped from the site to the patient
4. Remote monitoring and source data verification performed by the study monitor

Additional changes including, but not limited to drug holidays and deferral of imaging may be applied on a case-by case basis, as assessed necessary by the PI.

All temporary study changes will be discussed with the patient and documented in the site file.

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The **Medicines** for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 1031)

COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. *Official Journal of the European Union L 91/13*

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18. APPENDICES

18.1 APPENDIX 1: WHO PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry out all normal activity without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

18.2 APPENDIX 2: DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975,
and
the 35th World Medical Assembly, Venice, Italy, October 1983
and
the 41st World Medical Assembly, Hong-Kong, September 1989
and
the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research that may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research

involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I - BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time.

The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II - <u>MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)</u>

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best-proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent Committee (1,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III - NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

18.3 APPENDIX 3: MEASUREMENT OF DISEASE

Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1)

[Eisenhauer, 2009]

Baseline documentation of target and non-target lesions

- All baseline lesion assessments must be performed within 28 days of randomizations.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but 10mm short axis are considered non measurable.
- Pathological lymph nodes with 15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Efficacy assessment

Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) [Eisenhauer, 2009].

See the Time and Events Table (Section 3.8) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post baseline assessments, a window of 14 days is permitted to allow for flexible scheduling.

- The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis and clinical disease assessment for palpable lesions, brain scan and bone scan. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required

except for brain scan and bone scans. Brain and Bone scans should be performed as clinically indicated.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (*e.g*. evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

A baseline bone scan is required for all subjects with known bone metastases. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated (*e.g*. presentation of bone pain). For subjects with bone disease at baseline, a bone scan is required as clinically indicated. In addition, in order to assign a response of CR in a subject with bone disease at baseline, a bone scan must be performed within 1 week before or 4 weeks after the set of images showing CR in other sites of disease.

A baseline brain scan is only required for patients with known or suspected brain metastases. For subjects with CNS disease at baseline, a brain scan is required as clinically indicated. In addition, in order to confirm a CR in a subject with brain disease at baseline, a brain scan must be performed within 1 week before or 4 weeks after the 1st set of images showing CR in other sites of disease.

Assessment guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimetres (mm), using a ruler or callipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for on-going assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (*e.g*., skin nodules). In the case of skin lesions, documentation by colour photography, including a ruler/callipers to measure the size of the lesion, is required. [Eisenhauer, 2009].

CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended.

Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used. [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

Brain Scan: If baseline brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e., X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

Guidelines for Evaluation of Disease

Measurable and Non-measurable Definitions

Measurable lesion: A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (*e.g.*, if the slice thickness is 10 mm, a measurable lesion must be 20 mm).

10 mm calliper/ruler measurement by clinical exam or medical photography.

20 mm by chest x-ray.

Additionally, lymph nodes can be considered pathologically enlarged and measurable if 15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion: All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions. Note: non-measurable only disease is not allowed per protocol.

Response Criteria

Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (*e.g*. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (*e.g*. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (*e.g*. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (*e.g.* 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the

reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (*e.g*. <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (*e.g*. non-target response does not have to be "Not Evaluable").

New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Evaluation of overall response

Table 22 presents the overall response at an individual time point for all possible combinations of tumour responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 7: Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Note:

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined based on the investigators' assessment of response at each time point.

To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 4 weeks.

If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria (recommended):

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

18.4 APPENDIX 4: NEW YORK HEART ASSOCIATION (NYHA) SCALE

Class I – patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain)

Class II – patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain)

Class III – patients with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain)

Class IV – patients with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.

18.5 APPENDIX 5: LIST OF PROHIBITED DRUGS DURING THIS STUDY

CYP3A inhibitors		
Aprepitant	itraconazole	ketoconazole
clarithromycin	erythromycin	telithromycin
diltiazem	mifepristone	verapamil
Fluconazole	norfloxacin	voriconazole
Cimetidine (weak)	norfluoxetine	grapefruit, grapefruit juice or any product containing grapefruit
nelfinavir	nefazodone	Herbal remedies
Esomeprazole (weak)	Pantoprazole (weak)	Omeprazole (weak)
Indinavir	ritonavir	saquinavir
Palonosetron		
CYP3A inducers		
carbamazepine, oxcarbazepine	pioglitazone	rifampicin
dexamethasone and other glucocorticoids	phenobarbitone	rifapentine
felbamate	phenytoin	St. John's wort
modafinil	primidone	Troglitazone
nevirapine	rifabutin	
Sensitive CYP3A substrates with a Narrow Therapeutic Range		
alfentanil,	ergotamine,	sirolimus
aripiprazole	fentanyl	tacrolimus
astemizole	halofantrine	terfenadine
cisapride	pimozide	triazolam
cyclosporine	quinidine	

For a more extensive list please go to this website:

https://drug-interactions.medicine.iu.edu/MainTable.aspx

Medications which cause bradycardia or prolongation of the QT interval:

Crizotinib can cause prolongation of the QT interval and bradycardia. Co-treatment with other bradycardic agents, anti-arrhythmics or medications which prolong the QT interval should therefore be avoided. Examples are listed below:

Medicinal products known to prolong QT	Bradycardic agents
Anti-arrhthymics: Sotalol Quinine, Amiodarone, Disopyramide, Procainamide, Flecainide, Dofetilide	Non-hydropyridine calcium channel blockers (verapamil, diltiazem)
Antibiotics: Moxifloxacin, clarithromycin, ciprofloxacin, levofloxacin, Ofloxacin, Trimethorprim, Azithromycin, erythromycin	Beta-blockers
Anticonvulsants: Fosphenytoin, felbamate	Clonidine
Antidepressants: Mirtazapine, citalopram, venlafaxine, paroxetine, fluoxetine, sertraline, trazodone, escitalopram, clomipramine, amitriptyline, imipramine, nortryptyline, desimipramine, doxepin, trimipramine, protriptyline	Guanfacine
Anti-fungal: Voriconazole, fluconazole, ketoconazole, itraconazole	Digoxin
Antihistamines: Astemizole, terfenadine, diphenhydramine	Mefloquine
Anti-hypertensive: Nicardipine, israpidine, Moexipril	Anticholinesterases
Antipsychotic medications: Clozapine, ziprasidone, Thioridazine, risperidone, mesoridazine, quetiapine, haloperidol, pimozide, amisulpride, sertindole, iloperidone, paliperidone, chlorpromazine	Pilocarpine
Anti-emetics: Dolasetron, domperidone granisetron, levomepromazine, ondansetron, palonosetron	
Anti-malarials: Chloroquine, halofantrine, artenimol + piperaquine	
Anti-viral: Foscarnet, ritonavir, atazanavir	
Bronchodilators: Albuterol, salmeterol, metaproterenol, terbutaline, levalbuterol, ephedrine, phenylpropanolamine	
CNS stimulants: amphetamine, methylphenidate, dexmethylphenidate, lisdexfetamine	

Sedatives: Chloral hydrate, droperidol	
Miscellaneous: Alfuzosin, Amantadine, Atomoxitine ,Cisapride, Famotidine, Fingolimod, Indapamide, Ivabradine, Levomethadryl, Lithium, Mefloquine, Methadone, Midodrine, Mizolastine, Octreotide, Oxytocin, Pentamadine, Ritodrine, Sildenafil, Solifenacin, Tacrolimus, Tizanidine, Tolterodine, Vardenafil	

18.6 APPENDIX 6: POTENTIAL SIGHT-THREATENING EVENTS (PSTE) AND SEVERE VISION LOSS (SVL)

Based on US-FDA guidance, in all crizotinib-treated patients, Grade ≥2 PSTE (except for Visual field defect, for which Grade ≥3 is the standard) or SVL should be treated as Serious Adverse Events, regardless of relatedness to study drug. Please report these cases to the Sponsor and Pfizer, as specified in the protocol, within 24 hours of you or your staff member becoming aware of them.

The following MedDRA preferred terms are considered indicative of a PSTE or SVL event:

Amaurosis	Amaurosis fugax	Blindness
Blindness cortical	Blindness day	Blindness night
Blindness transient	Blindness unilateral	Hemianopia
Hemianopia heteronymous	Hemianopia homonymous	Optic atrophy
Optic ischaemic neuropathy	Optic nerve disorder	Optic neuropathy
Quadranopia	Retinopathy	Sudden visual (or vision) loss
Toxic optic neuropathy	Tunnel vision	Visual cortex atrophy
Visual field defect	Visual pathway disorder	Retinal oedema
Retinal detachment	Maculopathy	Iritis
Uveitis	Visual field test abnormal	

The occurrence of Grade ≥2 of any of these events should be treated as a SAE, except for Visual field defect, for which only Grade ≥3 should be treated as a SAE. Grade 2 events are considered to be PST and Grade ≥3 events are considered to be SVL.

18.7: Appendix 7: Amendment History

Protocol version/date	Reason for amendment
Version 1.0, 23/10/2017	-
Version 2.2, 11/12/2018	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 In Appendix 3 RECIST measurement of disease, the previous wording was incorrect therefore wording under section “Efficacy assessment” was amended. 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. • The position of the "Day 28+/- 3 days after last dose" column has been re-arranged and moved from the end column to follow the "after D1 of each cycle" column. • Added in wording "Follow Up" to the “Every 8 weeks until progression column” for clarity.
Version 3.0, 13/08/2020	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. Addition of two new investigator sites. Amendment to pregnancy prevention guidance following update to SmPC for fulvestrant IMP. Typographical, grammatical and formatting changes to the study protocol and patient information sheets. a. Changed ‘histologically’ to ‘histological’ for inclusion criterion 1 regarding diagnosis. b. Correction of referral in section 10.1.3 ‘Serious Adverse Events’ of the protocol. c. Update to inclusion criteria regarding creatinine clearance measured if creatinine is abnormal. d. Added ‘Streck’ tube alongside EDTA for collection of plasma samples in section 9.1.2 of the protocol.

	e. Typographical and formatting changes to the 'Schedule of events' table in section 8.5 of the protocol and the Patient Information Sheet. f. Numbered the tables throughout the protocol. g. Removed 'Survival' from 'Follow up' on the schedule of events table on the patient information sheets for both cohorts. h. Data Monitoring Committee (DMC) changed to Independent Data Monitoring Committee (IDMC) throughout the protocol. The assessment window for the 28 day Safety follow up visit is stated as +/- 3 days. List of prohibited medications and medications that cause bradycardia and prolong QT interval updated in Appendix 5. Addition of Amendment History as Appendix 7. Wording added to section 8.1.1 of the protocol to describe consent and recruitment of non-English speaking patients.
Version 4.0, dated 05/04/2022	1. Inclusion criterion 2 states that lobular breast cancer patients could have received either one line of chemotherapy or one line of therapy with CDK4/6 inhibitor. 2. Differentiated previous treatment between gastric cancer patients and triple negative lobular breast cancer or CDH1-mutated solid tumour patients. 3. Inclusion criterion for triple negative lobular breast cancer patients (basket cohort) and lobular breast cancer cohort patients updated to include E-cadherin negative status. 4. Added wording to section 4.2 of the protocol to align with section 15.1 that Safety Reviews are also required in the basket cohort too when 3 and 6 diffuse gastric cancer patients have been recruited. 5. Amended exclusion criterion 7 in section 5.1.2 of the protocol. The period of 12 days washout before the first dose of crizotinib changed to 5 half-lives for bradycardic agents, drugs which prolong the QT interval and/or anti-arrhythmic agents. 6. Instruction added to section 6.1 of the protocol for reduced starting dose of crizotinib for patients with documented Gilbert's disease. 7. Instructions added to Table 3 in section 6.2.1.1 of the protocol for management of non-haematological toxicities. 8. Glucose was already collected as part of the biochemistry tests at the screening 7 days visit. Now added to the text with the other biochemistry parameters on section 8.1.3 of the protocol. 9. Clarified that the biochemistry parameters required at day 1 of each cycle are required from cycle 2 onwards in section 8.2 of the protocol. 10. Definition of abnormal values that constitute reporting as adverse events has been clarified in section 10.1.1 of the protocol. 11. Section 16.9 'Off-site study procedures in case of crisis situation' added to the protocol to account for adjustments made in study conduct due to emergency situations such as the Covid-19 pandemic. Note added to section 8.2 to allow biochemistry tests to be performed locally at visits C1D8, C1D22, C2D8, C2D15 and C2D22 in cases of crisis situations.

	12. As biopsies should only be derived from metastatic tissue, the statement “diagnostic tumour” has been removed from section 9.1.1 of the protocol. Added statement that the sample can be from the primary tumour for patients presenting with de novo metastatic disease. 13. Reduced the systems required for physical examination at the evaluations within one week visit in section 8.1.3 of the protocol. 14. The baseline bone scan performed at baseline can be within 6 weeks prior to the first dose of treatment instead of 4 weeks. This instruction has been added to section 8.1.2 of the protocol for evaluations during screening and also Table 6 for the schedule of events. 15. Typographical and formatting changes.