Clinical trial results:
A Phase I/IIa trial of AZD4547 in combination with Cisplatin and Capecitabine (CX)

Summary

EudraCT number	2011-000642-37
Trial protocol	GB
Global end of trial date	12 January 2015

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	AZD4547-2011

Additional study identifiers

ISRCTN number	ISRCTN66171897
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Glasgow
Sponsor organisation address	University Avenue, GLASGOW, United Kingdom, G128QQ
Public contact	Dr Debra Stuart, University of Glasgow, 0141 3304539, debra.stuart@glasgow.ac.uk
Scientific contact	Dr Debra Stuart, University of Glasgow, 0141 3304539, debra.stuart@glasgow.ac.uk
Sponsor organisation name	NHS Greater Glasgow and Clyde
Sponsor organisation address	Clinical Research and Development Central Office, Ward 11, Dykebar Hospital, PAISLEY, United Kingdom, PA2 7DE
Public contact	Dr Margaret Fegen, NHS Greater Glasgow and Clyde, 0141 314 4011, margaret.fegen@ggc.scot.nhs.uk
Scientific contact	Dr Margaret Fegen, NHS Greater Glasgow and Clyde, 0141 314 4011, margaret.fegen@ggc.scot.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2015
Global end of trial reached?	Yes
Global end of trial date	12 January 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

(Stage 1) To identify a recommended dose of AZD4547 when administered in combination with Cisplatin and Capecitabine (CX).

(Stage 2) To determine the effect of AZD4547 in combination with Cisplatin and Capecitabine (AZD4547-CX) compared with Cisplatin and Capecitabine (CX) and placebo on progression-free survival (PFS) when administered to patients with locally advanced or metastatic gastro-oesophageal adenocarcinoma and with FGFR2 polysomy or amplification (FISH > 4)

Protection of trial subjects:

As part of the study patients required to attend for additional clinic visits and investigations which would be above those considered to be standard care. The visit schedule and number and tupe of investigations were fully explained to patients verbally and in writing via the patient information sheet to ensure patients were fully aware what was entailed in participating in the trial prior to them consenting to the study.

There were 2 parts to this study - Phase I (for all comers in solid tumours) and Phase IIa (for patients with advanced gastro-oesophageal adenocarcinoma whose tumours have FGFR2 polysomy or amplification). There were 3 separate patient information sheet and consent forms - 1 for Phase I patients only 1 for Phase IIa patients for testing of FSH status and 1 for Phase IIa patients consenting to randomisation into the main trial.

The patient information sheets fully explained the design of the study and that for Phase IIa patients - half the patient would receive AZD4547 and half would receive placebo in combination with cisplatin and capecitabine (for Phase I patients this was open label with no randomisation).

The side effects of all 3 study drugs were explained in the patient information sheet. All patients were closely monitored throughout the course of the study for adverse events and advised to report any side effects to their study nurse/doctor as they arose.

Background therapy:

Not Applicable

Evidence for comparator: -

Actual start date of recruitment	28 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Stage 1 part of the study opened to recruitment 01 March 2012. 19 patients were recruited into 3 cohorts. 16 were evaluable.
The Stage 2 part of the study opened to recruitment in September 2013 and was closed to recruitment on 12 January 2015. 41 patients were registered and 13 of these were randomised.

Pre-assignment

Screening details:

Patients underwent screening to ensure that that they met the eligibilty criteria. For Stage 1 they were then allocated a dose in the dose escalation phase.
Only patients with FISH 4/5 or FISH 6 tumours were considered for randomisation for the Stage 2 part of the study.

Period 1

Period 1 title	Stage 1 (Phase I) + Stage 2 (Phase II)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine

Arm description:

40mg BD AZD4547 with cisplatin and capecitabine

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg AZD4547 given twice daily in a days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

80 mg/m2 intravenously

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 orally twice daily on days 1 – 14

Arm title	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine

Arm description:

80mg BD AZD4547 with cisplatin and capecitabine

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

80 mg AZD4547 given twice daily in a days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m2 intravenously

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 orally twice daily on days 1 – 14

Arm title	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine

Arm description:

Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg AZD4547 given twice daily in a days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m2 intravenously

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 orally twice daily on days 1 – 14

Arm title	60mg BD AZD4547 with cisplatin and capecitabine

Arm description:

60mg BD AZD4547 with cisplatin and capecitabine

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg AZD4547 given twice daily on days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m2 intravenously

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 orally twice daily on days 1 – 14

Arm title	Placebo

Arm description:

Placebo BD with cisplatin and capecitabine

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

Dosage and administration details:

Placebo given twice daily on days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly (Stage II only)

Number of subjects in period 1	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine
Started	4	7	8
Completed	4	6	6
Not completed	0	1	2
Non-evaluable	-	1	2

Number of subjects in period 1	60mg BD AZD4547 with cisplatin and capecitabine	Placebo
Started	7	6
Completed	7	6
Not completed	0	0
Non-evaluable	-	-

Period 2

Period 2 title	Stage 1 (Phase I)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine

Arm description:

Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg AZD4547 given twice daily on days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

80 mg/m2 intravenously

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 orally twice daily on days 1 – 14

Arm title	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine

Arm description:

Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

80 mg AZD4547 given twice daily on days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m2 intravenously

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 orally twice daily on days 1 – 14

Arm title	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine

Arm description:

Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg AZD4547 given twice daily on days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m2 intravenously

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 orally twice daily on days 1 – 14

Number of subjects in period 2[1]	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine
Started	4	7	8
Completed	4	6	6
Not completed	0	1	2
Non-evaluable	-	1	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The trial is in 2 parts: Stage 1 (dose escalation) and Stage 2 (phase II/ dose expansion). Period 1 reports Stages 1 & 2 combined and therefore the periods do not follow on from each other.

Period 3

Period 3 title	Stage 2 (Phase II / dose expansion)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	60mg BD AZD4547 with cisplatin and capecitabine

Arm description:

60mg BD AZD4547 with cisplatin and capecitabine

Arm type	Experimental
Investigational medicinal product name	AZD4547
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg AZD4547 given twice daily in a days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m2 intravenously

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 orally twice daily on days 1 – 14

Arm title	Placebo

Arm description:

Placebo BD with cisplatin and capecitabine

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

Dosage and administration details:

Placebo given twice daily on days 1-14, 3-weekly oral administration schedule in combination with a fixed dose of Cisplatin (80 mg/m2 intravenously) and Capecitabine (1000 mg/m2 orally twice daily on days 1 – 14) three weekly

Number of subjects in period 3[2]	60mg BD AZD4547 with cisplatin and capecitabine	Placebo
Started	7	6
Completed	7	6

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The trial is in 2 parts: Stage 1 (dose escalation) and Stage 2 (phase II/ dose expansion). Period 1 reports Stages 1 & 2 combined and therefore the periods do not follow on from each other.

Baseline characteristics

Reporting groups	
Reporting group title	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: 40mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: 80mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	60mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: 60mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Placebo
Reporting group description: Placebo BD with cisplatin and capecitabine	

Reporting group values	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine
Number of subjects	4	7	8
Age categorical			
Age at study registration			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	5	5
From 65-84 years	1	2	3
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	2	4
Male	2	5	4

Reporting group values	60mg BD AZD4547 with cisplatin and capecitabine	Placebo	Total
Number of subjects	7	6	32

Age categorical			
Age at study registration			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	2	19
From 65-84 years	3	4	13
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	2	0	10
Male	5	6	22

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All evaluable patients (n=16) from Stage 1 and patients randomised (n=13) in Stage 2.	
Subject analysis set title	60mg AZD4547 (phase I + II)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients receiving 60mg AZD4547 in phase I or phase II	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Placebo arm from phase II	

Reporting group values	ITT	60mg AZD4547 (phase I + II)	Placebo
Number of subjects	29	12	6
Age categorical			
Age at study registration			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	8	2
From 65-84 years	12	5	4
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	9	5	0
Male	20	8	6

End points

End points reporting groups

Reporting group title	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: 40mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: 80mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	60mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: 60mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Placebo
Reporting group description: Placebo BD with cisplatin and capecitabine	
Reporting group title	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	60mg BD AZD4547 with cisplatin and capecitabine
Reporting group description: 60mg BD AZD4547 with cisplatin and capecitabine	
Reporting group title	Placebo
Reporting group description: Placebo BD with cisplatin and capecitabine	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All evaluable patients (n=16) from Stage 1 and patients randomised (n=13) in Stage 2.	
Subject analysis set title	60mg AZD4547 (phase I + II)
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients receiving 60mg AZD4547 in phase I or phase II	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo arm from phase II	

Primary: Stage 1 (Phase I) Primary analysis - MTD

End point title	Stage 1 (Phase I) Primary analysis - MTD[1]

End point description:

The maximum tolerated dose of AZD4547 in combination with Cisplatin and Capecitabine is defined as the highest dose at which < 2 of 6 patients experience dose limiting toxicity (DLT) with the first 3-week cycle of study treatment.
Dose limiting toxicity was based on the clinical and laboratory toxicity assessments (NCI-CTC version 4.02; Appendix 5):

- Grade IV neutropenia lasting for >7 days
- Grade III/IV neutropenia with sepsis or with fever > 38.5 0C
- Grade IV thrombocytopenia
- Grade IV diarrhoea
- Grade > III other non-haematological toxicities except for alopecia, and except for nausea or vomiting unless patients are taking optimal prophylaxis or supportive measures
- QTc prolongation > 500 msec or QTc increase > 60 msec above screening value
- Delay of > 2 weeks in administration of cycle 2 of treatment due to haematological or non-haematological toxicities
- Failure to de

End point type	Primary

End point timeframe:

DLTs in first 3-week cycle of study treatment to establish the MTD

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this is the Phase I part of the trial, the primary endpoint relates to descriptive data summaries.

End point values	Dose level 1: 40mg BD AZD4547 with cisplatin and capecitabine	Dose level 2: 80mg BD AZD4547 with cisplatin and capecitabine	Dose level -2: 60mg BD AZD4547 with cisplatin and capecitabine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	6	
Units: DLTs	0	2	1	

Attachments (see zip file)	DLTs by cohort/DLTs_by_cohort.bmp

Statistical analyses

No statistical analyses for this end point

Primary: Progression-free survival

End point title	Progression-free survival[2]

End point description:

Patients were evaluated for disease response every 9 weeks during chemotherapy with the same imaging methods (usually CT scanning) as used at the baseline (pre-chemotherapy) assessment of disease status. Patients in Stage 2 of the study continued to undergo disease response assessments at 9-week intervals after completion of up to 6 cycles of AZD4547-CX or placebo-CX until disease progression.

End point type	Primary

End point timeframe:

From registration/randomisation to confirmed progression or death.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this is the Phase I part of the trial, the primary endpoint relates to descriptive data summaries.

End point values	60mg AZD4547 (phase I + II)	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	6		
Units: Months				
median (confidence interval 80%)	6.844 (4.807 to 7.162)	6.121 (5.044 to 9.406)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent until resolution, or for at least 30 days after discontinuation of study medication, whichever comes first or until toxicity has resolved to baseline or < Grade 1, or until the toxicity is considered to be irreversible.

Adverse event reporting additional description:

Non-serious AEs reported according to worst grade so number of events equals the number of patients experiencing an event.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Dose level 1: 40mg BD AZD4547 (safety population)

Reporting group description:

40mg BD AZD4547 with cisplatin and capecitabine from phase I evaluable for safety population

Reporting group title	Dose level 2: 80mg BD AZD4547 (safety population)

Reporting group description:

80mg BD AZD4547 with cisplatin and capecitabine from phase I evaluable for safety population

Reporting group title	60mg BD AZD4547 (safety population)

Reporting group description:

60mg BD AZD4547 with cisplatin and capecitabine from phase I and II evaluable for safety population

Reporting group title	Placebo (safety population)

Reporting group description:

Placebo patients evaluable for safety population

Serious adverse events	Dose level 1: 40mg BD AZD4547 (safety population)	Dose level 2: 80mg BD AZD4547 (safety population)	60mg BD AZD4547 (safety population)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	3 / 7 (42.86%)	10 / 13 (76.92%)
number of deaths (all causes)	4	7	11
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignancy and unspecified - other			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboembolic event			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Cardiac troponin T increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Depresed level of consciousness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	3 / 13 (23.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Esophageal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders - other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	3 / 13 (23.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomach pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	3 / 13 (23.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal and urinary disorders - other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness lower limb			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lung infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo (safety population)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignancy and unspecified - other			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thromboembolic event			

subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Cardiac troponin T increased			

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Creatinine increased				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Depresed level of consciousness				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				

subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				

subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Esophageal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders - other			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stomach pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders - other			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle weakness lower limb			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dose level 1: 40mg BD AZD4547 (safety population)	Dose level 2: 80mg BD AZD4547 (safety population)	60mg BD AZD4547 (safety population)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	7 / 7 (100.00%)	13 / 13 (100.00%)
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	5 / 13 (38.46%)
occurrences (all)	0	2	5
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 4 (75.00%)	6 / 7 (85.71%)	12 / 13 (92.31%)
occurrences (all)	3	6	12
Fever			
subjects affected / exposed	0 / 4 (0.00%)	4 / 7 (57.14%)	2 / 13 (15.38%)
occurrences (all)	0	4	2
Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	1 / 4 (25.00%)	3 / 7 (42.86%)	2 / 13 (15.38%)
occurrences (all)	1	3	2
Cough			
subjects affected / exposed	2 / 4 (50.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	2	0	2
Dyspnea			
subjects affected / exposed	1 / 4 (25.00%)	3 / 7 (42.86%)	0 / 13 (0.00%)
occurrences (all)	1	3	0
Productive cough			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Sore throat			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Investigations			
White blood cell count decreased	Additional description: Cannot differentiate between grade 0 and 1 as lower limit of normal not available so reporting considers grade 2 and above as an occurence.		
subjects affected / exposed	1 / 4 (25.00%)	4 / 7 (57.14%)	8 / 13 (61.54%)
occurrences (all)	1	4	8
Platelet count decreased	Additional description: Cannot differentiate between grade 0 and 1 as lower limit of normal not available so reporting considers grade 2 and above as an occurrence.		
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	4 / 13 (30.77%)
occurrences (all)	0	1	4
Neutrophil count decreased	Additional description: Cannot differentiate between grade 0 and 1 as lower limit of normal not available so reporting considers grade 2 and above as an occurrence.		
subjects affected / exposed	1 / 4 (25.00%)	5 / 7 (71.43%)	7 / 13 (53.85%)
occurrences (all)	1	5	7
Alkaline phosphatase increased			
subjects affected / exposed	3 / 4 (75.00%)	5 / 7 (71.43%)	5 / 13 (38.46%)
occurrences (all)	3	5	5
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 4 (50.00%)	2 / 7 (28.57%)	3 / 13 (23.08%)
occurrences (all)	2	2	3
Alanine aminotransferase increased			
subjects affected / exposed	2 / 4 (50.00%)	2 / 7 (28.57%)	5 / 13 (38.46%)
occurrences (all)	2	2	5
Creatinine increased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Weight loss			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	4 / 13 (30.77%)
occurrences (all)	0	0	4
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Cardiac troponin T increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	1	0	2
Peripheral motor neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	2 / 13 (15.38%)
occurrences (all)	1	1	2
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	3 / 7 (42.86%)	2 / 13 (15.38%)
occurrences (all)	0	3	2
Dizziness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	3 / 13 (23.08%)
occurrences (all)	1	0	3
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 7 (42.86%)	2 / 13 (15.38%)
occurrences (all)	0	3	2
Dysphasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Syncope			

subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia	Additional description: Cannot differentiate between grade 0 and 1 as lower limit of normal not available so reporting considers grade 2 and above as an occurence.		
subjects affected / exposed	2 / 4 (50.00%)	3 / 7 (42.86%)	10 / 13 (76.92%)
occurrences (all)	2	3	10
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Hearing loss			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	5 / 13 (38.46%)
occurrences (all)	0	2	5
Ear and labyrinth disorders - other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	3 / 13 (23.08%)
occurrences (all)	1	1	3
Dry eye			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Punctuate keratopathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Eye disorders - other			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	3 / 13 (23.08%)
occurrences (all)	1	0	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 4 (50.00%)	6 / 7 (85.71%)	11 / 13 (84.62%)
occurrences (all)	2	6	11

Mucositis oral			
subjects affected / exposed	2 / 4 (50.00%)	6 / 7 (85.71%)	10 / 13 (76.92%)
occurrences (all)	2	6	10
Diarrhoea			
subjects affected / exposed	3 / 4 (75.00%)	6 / 7 (85.71%)	5 / 13 (38.46%)
occurrences (all)	3	6	5
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	3 / 7 (42.86%)	7 / 13 (53.85%)
occurrences (all)	2	3	7
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	5 / 7 (71.43%)	9 / 13 (69.23%)
occurrences (all)	0	5	9
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	3 / 7 (42.86%)	2 / 13 (15.38%)
occurrences (all)	1	3	2
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	3 / 13 (23.08%)
occurrences (all)	0	0	3
Gastrointestinal disorders - other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Dyspepsia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	3 / 13 (23.08%)
occurrences (all)	1	2	3
Alopecia			

subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Abnormal growth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders - other			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Renal and urinary disorders - other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders - other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Infections and infestations			
Lung infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Penile infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	3 / 4 (75.00%)	3 / 7 (42.86%)	8 / 13 (61.54%)
occurrences (all)	3	3	8
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Hypokalaemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	5 / 13 (38.46%)
occurrences (all)	1	2	5
Hypercalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	3 / 13 (23.08%)
occurrences (all)	1	1	3
Hypoalbuminaemia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 7 (28.57%)	7 / 13 (53.85%)
occurrences (all)	2	2	7
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Hypermagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	1	0	2
Hypomagnesaemia			
subjects affected / exposed	2 / 4 (50.00%)	6 / 7 (85.71%)	10 / 13 (76.92%)
occurrences (all)	2	6	10
Anorexia			
subjects affected / exposed	2 / 4 (50.00%)	4 / 7 (57.14%)	6 / 13 (46.15%)
occurrences (all)	2	4	6
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 7 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2

Non-serious adverse events	Placebo (safety population)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		

Vascular disorders			
Thromboembolic event			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 5 (100.00%)		
occurrences (all)	5		
Fever			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dyspnea			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Sore throat			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Investigations			
White blood cell count decreased	Additional description: Cannot differentiate between grade 0 and 1 as lower limit of normal not available so reporting considers grade 2 and above as an occurence.		

subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Platelet count decreased	Additional description: Cannot differentiate between grade 0 and 1 as lower limit of normal not available so reporting considers grade 2 and above as an occurrence.		
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased	Additional description: Cannot differentiate between grade 0 and 1 as lower limit of normal not available so reporting considers grade 2 and above as an occurrence.		
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Alkaline phosphatase increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Weight loss			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Cardiac troponin T increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Peripheral motor neuropathy			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dysphasia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia	Additional description: Cannot differentiate between grade 0 and 1 as lower limit of normal not available so reporting considers grade 2 and above as an occurence.		
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Hearing loss			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders - other			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Tinnitus			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Punctuate keratopathy			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Eye disorders - other			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 5 (80.00%)		
occurrences (all)	4		
Mucositis oral			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dry mouth			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders - other			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Abnormal growth			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - other			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			

Renal and urinary disorders - other subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders - other subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Infections and infestations Lung infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Penile infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all) Hyperkalaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypercalcaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 5 (60.00%) 3 2 / 5 (40.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 2 / 5 (40.00%) 2 3 / 5 (60.00%) 3		

Blood bilirubin increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hypermagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	5 / 5 (100.00%)		
occurrences (all)	5		
Anorexia			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2011	Protocol Version 2 17th October 2011 Protocol updated in view of MHRA Grounds for Non-Acceptance •Section 6.1.3 amended to include the dose escalation information. •Page 35 amended to be consistent with the schedule of events on Page 9 (this now reads that serum phosphate, calcium and magnesium should be included in the standard clinical chemistry safety bloods which should be taken week for the first two treatment cycles and then weekly thereafter. •The Schedule of Events/Investigations on Page 9 amended so that the ECGs and assessment of the QTc are consistent with page 46 of the protocol. Patient information sheets also updated with this information
06 December 2011	Change in PI Christie Hospital from Professor Malcolm Ranson to Dr Fiona Thistlethwaite
20 August 2012	Protocol Version 3, 30th August 2012 •Non-negligent harm information updated on IRAS form and patient information sheets •Extension of time from consent to patient registration from 28 to 42 days. •Exclusion criteria for toxicities from previous treatments amended from > grade 1 to > grade 1. •Reporting of SAEs from consent only for SAEs relating to NIMPs •A new section (9.7 Reference Safety Information) has been added
07 March 2013	Protocol Version 4, 7th March 2013 •In order to optimise the maintenance monotherapy dose of AZD4547/placebo after completion of chemotherapy we have written into the protocol intrapatient dose escalation to a maximum of 80mg which was the maximum tolerated dose in the Phase I monotherapy study •There will no longer be the formulation of a 100mg tablet, this will now be an 80mg tablet (along with the 20mg tablet) •Clarification has been added to advise sites that there will be no exceptions to the eligibility criteria •A section has been added regarding Incident Reporting and Serious Breaches so that sites are aware of their responsibilities for reporting these •The reference safety information section has been updated •AstraZeneca have updated their guidelines for the management of RPED (Retinal Epithelial Detachment). There is now evidence that the condition is reversible and that it can be identified, monitored and managed. The protocol has been updated to include these guidelines (Figures 4, 5 and 6) •The time for the resolution of CTC grade 2 toxicities and raised calcium:phosphate product/serum phosphate from 14 days to 21 days before treatment recommences or the patient discontinues, in line with the time patients spend off treatment in the new RPED algorithm
13 August 2013	Addition of new sites: •Taunton and Somerset NHS Trust, Musgrove Park Hospital, PI Dr Emma Cattell •Guy's and St Thomas' NHS Trust, PI Dr Nick Maisey •Clatterbridge Cancer Centre NHS Foundation Trust, PI Dr Adrian Moss •University Hospitals Morecambe Bay Trust, PI Dr David Fyfe Change in PI, Hammersmith Hospital from Professor Hani Gabra to Dr Dani Power

04 September 2013	Protocol Version 5, 4th September 2013 •New Manufacturing Authorisation provided by AstraZeneca for their site in Molndal, Sweden •To allow for same day/research nurse consent for the FISH tumour testing part of the Stage 2 of the study •To allow for Troponin T to be measured as an alternative to Troponin I •Further administrative changes
14 November 2013	Addition of new sites: •Dr Alan Anthoney, The Leeds Teaching Hospitals NHS Trust, St James's University Hospital •Dr Liz Toy, Royal Devon & Exeter NHS Foundation Trust •Dr Srinivasan Madhusudan, Nottingham University Hospitals NHS Trust, City Hospital •Dr Tim Iveson, University Hospital Southampton NHS Foundation Trust, Southampton General Hospital •Dr Justin Waters, Maidstone & Tunbridge Wells NHS Trust, Maidstone Hospital Change in PI Belfast City Hospital from Dr Martin Eatock to Dr Colin Purcell
24 June 2014	Temporary Halt of Study: Shortly after commencing the randomised phase II part of the FACING, Astra Zeneca reviewed data from their own studies, and concluded that the selection biomarker for FGFR2, performed at Quintiles, Edinburgh was not robust for patient selection, and AZ no longer supported this patient selection assay. We were offered to establish our own patient selection assay in an academic environment, but given the complexity of this and the very challenging timescales given to us by AZ, this became impossible and the study was closed prematurely after only a small proportion of the planned patient sample size had been enrolled.
19 November 2014	Addition of new site: •Charing Cross Hospital, Imperial Healthcare NHS Trust, PI Dr Danielle Power Changes in PI: •Clatterbridge Centre for Oncology previous PI Dr Adrian Moss, new PI Dr Ayman Madi •Belfast City Hospital previous PI Dr Colin Purcell, new PI Dr Richard Turkingston

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

09 June 2014	Shortly after commencing the randomised phase II part of the FACING, Astra Zeneca reviewed data from their own studies, and concluded that the selection biomarker for FGFR2, performed at Quintiles, Edinburgh was not robust for patient selection, and AZ no longer supported this patient selection assay. We were offered to establish our own patient selection assay in an academic environment, but given the complexity of this and the very challenging timescales given to us by AZ, this became impossible and the study was closed prematurely after only a small proportion of the planned patient sample size had been enrolled.	-

Notes:

Limitations and caveats

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

Due to the early termination of this study, only 13/140 patients were randomised to the Phase IIa part of the study.

Notes: