Clinical trial results:
FGFR Inhibition for Epithelial Solid Tumours: a Phase Ib trial of AZD4547 in combination with gemcitabine and cisplatin

Summary

EudraCT number	2011-004072-10
Trial protocol	GB
Global end of trial date	24 October 2017

Results information

Result version number	v1 (current)
This version publication date	31 August 2019
First version publication date	31 August 2019

Trial information

Trial identification

Sponsor protocol code	MO11/9803

Additional study identifiers

ISRCTN number	ISRCTN44149443
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	University of Leeds, Leeds, United Kingdom, LS2 9JT
Public contact	Clinical Trials Research Unit, University of Leeds, +44 01133439141, medctfst@leeds.ac.uk
Scientific contact	Clinical Trials Research Unit, University of Leeds, +44 01133439141, medctfst@leeds.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2016
Global end of trial reached?	Yes
Global end of trial date	24 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Dose Escalation Cohort
To investigate the safety, tolerability and feasibility of the novel AGC (AZD4547 with gemcitabine and cisplatin) combination in advanced non-haematological malignancies.

Randomised Expansion Cohort
To obtain a preliminary indication of the relative toxicities of AGC compared to GC in locally-advanced/metastatic TCC of the urinary bladder (and other urothelial) cancers.

Protection of trial subjects:

Patients were monitored regularly throughout trial treatment and may have required extra hospital visits. Every effort was made to schedule appointments for tests to coincide with scheduled visits to the hospital.
Extra blood samples may have been required for the trial at some appointments, some of these required additional needle punctures but were carried out at the same testing point where possible.
Potential side effects of treatment were explained to patients in the Patient Information Sheet.
Treatment modifications and supportive care could be given to minimise these.
An ophthalmology exam was performed that may include inserting paper in the eye for 5 minutes. This was carried out by a qualified ophthalmologist as a standard test.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 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: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	17
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were identified in routine clinic visits at NHS hospitals running the trial. Patients were consented and registered. Screening tests performed and treatment began.

Pre-assignment

Screening details:

Participants underwent screening to ensure they met the eligibility criteria including ophthalmology examination and isotopic GFR. They were then allocated a dose in the dose escalation phase or randomised in the expanded phase.

Period 1

Period 1 title	Dose Escalation Cohort
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: GC & AZD4547 40mg BD

Arm description:

Gemcitabine, Cisplatin, AZD4547 at 40mg BD

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:

40mg twice daily, oral doses of AZD4547 for 14 days at the beginning of each 21-day cycle, for up to 6 cycles.

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

Dosage and administration details:

1000mg/m2 (IV days 1 & 8 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 30-60 minutes, before Cisplatin

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

Dosage and administration details:

70mg/m2 (IV day 1 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 2-4 hours

Arm title	Dose level 2: GC & AZD4547 80mg BD

Arm description:

Gemcitabine, Cisplatin and AZD4547 at 80mg BD

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:

80mg twice daily, oral doses of AZD4547 for 14 days at the beginning of each 21-day cycle, for up to 6 cycles.

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

Dosage and administration details:

1000mg/m2 (IV days 1 & 8 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 30-60 minutes, before Cisplatin

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

Dosage and administration details:

70mg/m2 (IV day 1 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 2-4 hours

Arm title	Dose level 3: GC & AZD4547 100mg BD

Arm description:

Gemcitabine, Cisplatin and AZD4547 at 100mg BD

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:

100mg twice daily, oral doses of AZD4547 for 14 days at the beginning of each 21-day cycle, for up to 6 cycles.

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

Dosage and administration details:

1000mg/m2 (IV days 1 & 8 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 30-60 minutes, before Cisplatin

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

Dosage and administration details:

70mg/m2 (IV day 1 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 2-4 hours

Number of subjects in period 1	Dose level 1: GC & AZD4547 40mg BD	Dose level 2: GC & AZD4547 80mg BD	Dose level 3: GC & AZD4547 100mg BD
Started	4	6	9
Completed	4	6	9

Period 2	
Period 2 title	Randomised Expansion Cohort
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	AZD4547, Gemcitabine + Cisplatin

Arm description:

AZD4547, Gemcitabine, Cisplatin

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:

80mg twice daily, oral doses of AZD4547 for 14 days at the beginning of each 21-day cycle, for up to 6 cycles.

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

Dosage and administration details:

1000mg/m2 (IV days 1 & 8 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 30-60 minutes, before Cisplatin

for the randomised expansion phase, therefore was included in the randomised expansion analysis population as per the trial definition.

Period 3

Period 3 title	Baseline
Is this the baseline period?	Yes[3]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Dose escalation

Arm description:

Gemcitabine, Cisplatin, AZD4547 at 40mg BD - 100mg BD
Includes one patient receiving AZD4547 at 80mg BD who is also included in the randomised expansion group due to being eligible for analysis in this group.

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:

40mg - 100mg (escalating cohorts) twice daily, oral doses of AZD4547 for 14 days at the beginning of each 21-day cycle, for up to 6 cycles.

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

Dosage and administration details:

1000mg/m2 (IV days 1 & 8 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 30-60 minutes, before Cisplatin

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

Dosage and administration details:

70mg/m2 (IV day 1 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 2-4 hours

Arm title	Randomised expansion

Arm description:

Randomised expansion analysis population: 9 patients randomised plus one patient who received AGC at the RDST in the escalation phase who fulfilled the eligibility criteria for expansion.

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

Dosage and administration details:

80mg twice daily, oral doses of AZD4547 for 14 days at the beginning of each 21-day cycle, for up to 6 cycles. [ACG arm only]

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

Dosage and administration details:

1000mg/m2 (IV days 1 & 8 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 30-60 minutes, before Cisplatin

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

Dosage and administration details:

70mg/m2 (IV day 1 of each 21-day cycle, for up to 6 cycles)
To be given by IV infusion over 2-4 hours

Notes:

[3] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The trial analysis is undertaken in two components: dose escalation and randomised expansion. Therefore neither period 1 or 2 are baseline, rather both are. As such, both had to be entered into a separate "period", period 3.

Number of subjects in period 3	Dose escalation	Randomised expansion
Started	19	10
Completed	19	10

Baseline characteristics

Reporting groups	
Reporting group title	Dose escalation
Reporting group description:	
Gemcitabine, Cisplatin, AZD4547 at 40mg BD - 100mg BD Includes one patient receiving AZD4547 at 80mg BD who is also included in the randomised expansion group due to being eligible for analysis in this group.	
Reporting group title	Randomised expansion
Reporting group description:	
Randomised expansion analysis population: 9 patients randomised plus one patient who received AGC at the RDST in the escalation phase who fulfilled the eligibility criteria for expansion.	

Reporting group values	Dose escalation	Randomised expansion	Total
Number of subjects	19	10	28
Age categorical 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)	11	7	17
From 65-84 years	8	3	11
85 years and over	0	0	0
Age continuous Units: years			
median	58	61	
full range (min-max)	39 to 75	50 to 81	-
Gender categorical Units: Subjects			
Female	8	2	9
Male	11	8	19
Type of Cancer Units: Subjects			
TCC Bladder	3	8	10
TCC Urinary Tract	0	1	1
Other	16	1	17
Number of target lesions Units: number of lesions			
median	2	1.5	
full range (min-max)	0 to 5	0 to 2	-
Time from most recent relapse/progression to registration Units: Months			
median	2.5	1.4	
full range (min-max)	0.5 to 30.8	1 to 2.7	-

End points

End points reporting groups

Reporting group title	Dose level 1: GC & AZD4547 40mg BD
Reporting group description: Gemcitabine, Cisplatin, AZD4547 at 40mg BD	
Reporting group title	Dose level 2: GC & AZD4547 80mg BD
Reporting group description: Gemcitabine, Cisplatin and AZD4547 at 80mg BD	
Reporting group title	Dose level 3: GC & AZD4547 100mg BD
Reporting group description: Gemcitabine, Cisplatin and AZD4547 at 100mg BD	
Reporting group title	AZD4547, Gemcitabine + Cisplatin
Reporting group description: AZD4547, Gemcitabine, Cisplatin	
Reporting group title	Gemcitabine + Cisplatin
Reporting group description: Gemcitabine, Cisplatin	
Reporting group title	Dose escalation
Reporting group description: Gemcitabine, Cisplatin, AZD4547 at 40mg BD - 100mg BD Includes one patient receiving AZD4547 at 80mg BD who is also included in the randomised expansion group due to being eligible for analysis in this group.	
Reporting group title	Randomised expansion
Reporting group description: Randomised expansion analysis population: 9 patients randomised plus one patient who received AGC at the RDST in the escalation phase who fulfilled the eligibility criteria for expansion.	

Primary: DLTs, within the first cycle (until cycle 2, day 1), in order to establish the MTD of AZD4547 in combination with GC

End point title	DLTs, within the first cycle (until cycle 2, day 1), in order to establish the MTD of AZD4547 in combination with GC[1]
End point description: Maximum Tolerated Dose: the highest dose level at which no more than 1 participant experiences a DLT, during the first cycle of treatment i.e. the dose level below that at which 2 or more participants experiences a DLT. Dose-Limiting Toxicities: • Complicated grade 4 neutropenia with fever >38oC and/or haemodynamic compromise • Absolute Neutrophil Count (ANC) <0.5 x 109/L lasting for 7 days or more • Grade 4 thrombocytopenia (platelets <25 x 109/L) lasting for 7 days or more • Grade 3 or 4 thrombocytopenia (platelets <50 x 109/L) with significant active bleeding • Any unexpected grade 3 or 4 non-haematological toxicity that is considered related to treatment. • Hyperphosphataemia (serum phosphate level above 4.5 mmol/l or > 56 mg/dl) • Delay of commencement of 2nd cycle by more than 14 days, due to significant toxicity or tolerability issue • Any other event which, in the opinion of the SRC, is considered to be clinically significant and related to treatment	
End point type	Primary
End point timeframe: Within the first cycle, up to cycle 2 day 1	

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 a phase I study, the primary endpoint relates to data summaries only.

End point values	Dose level 1: GC & AZD4547 40mg BD	Dose level 2: GC & AZD4547 80mg BD	Dose level 3: GC & AZD4547 100mg BD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[2]	6	6[3]	
Units: Number of DLTs				
Unexpected grade 3 or 4 non-haematological tox	0	0	1	
No DLT	4	5	4	
Grade 4 thrombocytopenia	0	1	0	
Grade 3/4 thrombocytopenia with bleeding	0	0	1	

Notes:

[2] - 1 patient received <80% of one treatment cycle so unevaluable for DLTs

[3] - 3 patients received <80% of one treatment cycle so unevaluable for DLTs

Statistical analyses

No statistical analyses for this end point

Primary: CTCAE grade 3 or 4 toxicity within the first 3 cycles of treatment to determine the RDST

End point title	CTCAE grade 3 or 4 toxicity within the first 3 cycles of treatment to determine the RDST[4]

End point description:

Maximum CTCAE grade of each AE reported.

Definition of Recommended Dose for Sustained Tolerability
Once the MTD has been established, a minimum of 6 participants will be treated at this dose level in order to establish the RDST. The RDST will be defined as:

The highest dose level at which 3 or more of 6 evaluable participants complete 3 or more consecutive cycles without toxicity which, in the opinion of the Safety Review Committee, is clinically significant, unacceptable and attributable to the addition of AZD4547 to gemcitabine and cisplatin.

The RDST will be determined by the Safety Review Committee upon review of toxicities observed throughout cycles 1-3, along with any other safety data which are deemed clinically relevant.

End point type	Primary

End point timeframe:

Within first 3 cycles of treatment.

Notes:

[4] - 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 a phase I study, the primary endpoint relates to data summaries only.

End point values	Dose level 1: GC & AZD4547 40mg BD	Dose level 2: GC & AZD4547 80mg BD	Dose level 3: GC & AZD4547 100mg BD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	6	9	
Units: Number of participants				
Grade 2	2	0	3	
Grade 3	2	2	2	

Grade 4	0	4	4	

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of participants treated who experience any grade 3 or 4 CTCAE toxicity throughout all treatment cycles

End point title	Proportion of participants treated who experience any grade 3 or 4 CTCAE toxicity throughout all treatment cycles[5]

End point description:

The proportion of participants treated who experience any grade 3 or 4 CTCAE toxicity will be calculated as number of participants who experience any grade 3 or 4 CTCAE toxicity throughout their treatment cycle in each arm, as a proportion of those participants who receive at least one dose of study treatment within each arm.

Maximum CTCAE grade of AE reported across all treatment cycles.

End point type	Primary

End point timeframe:

All treatment cycles

Notes:

[5] - 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 a phase I study, the primary endpoint relates to data summaries only.

End point values	AZD4547, Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of patients				
Grade 2	0	1		
Grade 3	2	2		
Grade 4	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate and disease control rate

End point title	Objective response rate and disease control rate

End point description:

Objective response = complete response or partial response
Disease control = complete response, partial response or stable disease

End point type	Secondary

End point timeframe:

Within the treatment period

End point values	AZD4547, Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[6]	5		
Units: Number of patients				
Complete response	1	1		
Partial response	0	2		
Stable disease	2	1		
Non CR / non PD (no target lesions)	0	1		
Clinical progression	1	0		
No scan performed, not clinically progressed	1	0		

Notes:

[6] - Includes patient receiving AGC at RDST in escalation and eligible for expansion

Statistical analyses

No statistical analyses for this end point

Secondary: Change in tumour size

End point title	Change in tumour size

End point description:

Change in tumour size is defined as change from baseline assessment. Presented as change from baseline to best response (i.e. largest decrease, or smallest increase from baseline).

End point type	Secondary

End point timeframe:

Within the treatment period

End point values	AZD4547, Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[7]	5		
Units: Difference in tumour size, mm				
-1mm	1	0		
-14mm	1	0		
-4mm	1	0		
+4mm	0	1		
-37mm	0	1		
-22mm	0	1		
-53.9mm	0	1		
No scan performed	2	0		
No target lesions	0	1		

Notes:

[7] - Includes patient receiving AGC at the RDST in the escalation phase and eligible for expansion

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival is defined as the time from dose allocation/randomisation to first documented evidence of disease progression or death. Participants who, at the time of analysis, have not progressed will be censored at the last date they were known to be alive and progression free.

End point type	Secondary

End point timeframe:

From dose allocation or randomisation until disease progression or death.

End point values	AZD4547, Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[8]	5		
Units: Months				
median (confidence interval 95%)	6.47 (0.39 to 12.6)	11.4 (4.83 to 11.4)		

Notes:

[8] - Includes patient receiving AGC at the RDST in the escalation phase and eligible for expansion

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival is defined as the time from randomisation to date of death from any cause. Participants who are still alive at the time of analysis will be censored at the last date they were known to be alive.

N.B -9999999999=-Inf and 9999999999=Inf

End point type	Secondary

End point timeframe:

From randomisation (or dose allocation) to death.

End point values	AZD4547, Gemcitabine + Cisplatin	Gemcitabine + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[9]	5		
Units: Months				
median (confidence interval 95%)	8.57 (0.39 to 9999999999)	12.7 (-9999999999 to 9999999999)		

Notes:

[9] - Includes patient receiving AGC at the RDST in the escalation phase and eligible for expansion

Statistical analyses

No statistical analyses for this end point

Secondary: Withdrawals from treatment

End point title	Withdrawals from treatment

End point description:

End point type	Secondary

End point timeframe:

Throughout treatment

End point values	Dose level 1: GC & AZD4547 40mg BD	Dose level 2: GC & AZD4547 80mg BD	Dose level 3: GC & AZD4547 100mg BD	AZD4547, Gemcitabine + Cisplatin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	6	9	5[10]
Units: Number of patients				
Withdrawn from treatment	1	0	0	0

Notes:

[10] - Includes patient receiving AGC at the RDST in the escalation phase and eligible for expansion

End point values	Gemcitabine + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of patients				
Withdrawn from treatment	0			

Statistical analyses

No statistical analyses for this end point

Secondary: FGFR3 expression

End point title	FGFR3 expression

End point description:

End point type	Secondary

End point timeframe:
At entry to trial

End point values	Dose level 1: GC & AZD4547 40mg BD	Dose level 2: GC & AZD4547 80mg BD	Dose level 3: GC & AZD4547 100mg BD	AZD4547, Gemcitabine + Cisplatin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[11]	1[12]	4[13]	2[14]
Units: Number of patients				
0: all negative	0	1	1	0
1: faint but detectable	1	0	2	0
2: weak but extensive postivity	0	0	0	2
3: strong positivity	0	0	0	0
Some 3, mostly 1	0	0	1	0

Notes:
[11] - Expression only gained for 1 patient
[12] - Expression only gained for 1 patient
[13] - Expression only gained for 4 patients
[14] - Expression only gained for 2 patients

End point values	Gemcitabine + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	1[15]			
Units: Number of patients				
0: all negative	0			
1: faint but detectable	0			
2: weak but extensive postivity	0			
3: strong positivity	1			
Some 3, mostly 1	0			

Notes:
[15] - Expression only gained for 1 patient

Statistical analyses

No statistical analyses for this end point

Secondary: FGFR3 mutation status

End point title	FGFR3 mutation status

End point description:

End point type	Secondary

End point timeframe:
At entry to trial

End point values	Dose level 1: GC & AZD4547 40mg BD	Dose level 2: GC & AZD4547 80mg BD	Dose level 3: GC & AZD4547 100mg BD	AZD4547, Gemcitabine + Cisplatin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[16]	1[17]	3[18]	2[19]
Units: Number of patients				
wild-type	1	1	3	2
mutant (S249C)	0	0	0	0

Notes:

[16] - Mutation status only gained for 1 patient

[17] - Mutation status only gained for 1 patient

[18] - Mutation status only gained for 3 patients

[19] - Mutation status only gained for 2 patients

End point values	Gemcitabine + Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	1[20]			
Units: Number of patients				
wild-type	0			
mutant (S249C)	1			

Notes:

[20] - Mutation status only gained for 1 patient

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs: from the time of written informed consent until 28 days following dosing with an IMP.
SARs and SUSARs: from the time of written informed consent until the end of the trial.

Adverse event reporting additional description:

Reporting of AEs prompted on CRFs at day 8 and 15 of each treatment cycle, and at the end of treatment.
Due to the way events collected on the trial:
1. SAEs are also reported as AEs
2. For AEs, the number of occurrences is equal to the number of patients apart from "other" events where each event under other is listed once per patient

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Dose level 1: GC + AZD4547 40mg BD
Reporting group description: -	
Reporting group title	Dose level 2: GC + AZD4547 80mg BD
Reporting group description: -	
Reporting group title	Dose level 3: GC + AZD4547 100mg BD
Reporting group description: -	
Reporting group title	AZD4547, Gemcitabine + Cisplatin
Reporting group description:	
AGC analysis population, including 1 patient receiving AGC at the RDST in the dose escalation phase.	
Reporting group title	Gemcitabine + Cisplatin
Reporting group description: -	

Serious adverse events	Dose level 1: GC + AZD4547 40mg BD	Dose level 2: GC + AZD4547 80mg BD	Dose level 3: GC + AZD4547 100mg BD
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	3 / 6 (50.00%)	4 / 9 (44.44%)
number of deaths (all causes)	2	2	3
number of deaths resulting from adverse events	0	0	0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 9 (22.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thromboembolic event			

subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (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
Nervous system disorders			
Stroke			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (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			
Ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (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
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			

subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 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 / 6 (0.00%)	0 / 9 (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
Infections and infestations			
Other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (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
Lung infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
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			
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (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

Serious adverse events	AZD4547, Gemcitabine + Cisplatin	Gemcitabine + Cisplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	1 / 5 (20.00%)	
number of deaths (all causes)	4	2	
number of deaths resulting from adverse events	1	0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Other			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dose level 1: GC + AZD4547 40mg BD	Dose level 2: GC + AZD4547 80mg BD	Dose level 3: GC + AZD4547 100mg BD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	6 / 6 (100.00%)	9 / 9 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Phlebitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Thromboembolic event			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	1 / 9 (11.11%)
occurrences (all)	1	2	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0

Oedema limbs			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	2 / 9 (22.22%)
occurrences (all)	1	1	2
Fatigue			
subjects affected / exposed	3 / 4 (75.00%)	5 / 6 (83.33%)	7 / 9 (77.78%)
occurrences (all)	3	5	7
Fever			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	2 / 4 (50.00%)	2 / 6 (33.33%)	1 / 9 (11.11%)
occurrences (all)	2	2	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Testicular pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	3 / 9 (33.33%)
occurrences (all)	2	1	3
Hiccups			

subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hoarseness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Confusion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	5 / 6 (83.33%)	4 / 9 (44.44%)
occurrences (all)	1	5	4
Alkaline phosphatase increased			
subjects affected / exposed	1 / 4 (25.00%)	3 / 6 (50.00%)	4 / 9 (44.44%)
occurrences (all)	1	3	4
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
GGT increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Other			
subjects affected / exposed	1 / 4 (25.00%)	5 / 6 (83.33%)	6 / 9 (66.67%)
occurrences (all)	2	8	11
Platelet count decreased			

subjects affected / exposed	1 / 4 (25.00%)	6 / 6 (100.00%)	7 / 9 (77.78%)
occurrences (all)	1	6	7
Weight loss			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	1 / 9 (11.11%)
occurrences (all)	1	2	1
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	6 / 6 (100.00%)	7 / 9 (77.78%)
occurrences (all)	0	6	7
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Aphonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Dysgeusia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	1 / 9 (11.11%)
occurrences (all)	1	2	1
Headache			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Other			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Olfactory nerve disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	3 / 9 (33.33%)
occurrences (all)	1	1	3
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Stroke			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)	6 / 6 (100.00%)	8 / 9 (88.89%)
occurrences (all)	1	6	8
Leukocytosis			
subjects affected / exposed	1 / 4 (25.00%)	3 / 6 (50.00%)	5 / 9 (55.56%)
occurrences (all)	1	3	5
Ear and labyrinth disorders			
Other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hearing impaired			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	2 / 9 (22.22%)
occurrences (all)	1	2	2
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Other			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Glaucoma			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Retinal detachment			
subjects affected / exposed	0 / 4 (0.00%)	4 / 6 (66.67%)	5 / 9 (55.56%)
occurrences (all)	0	4	5
Watering eyes			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	3 / 6 (50.00%)	3 / 9 (33.33%)
occurrences (all)	1	3	3
Cheilitis			
subjects affected / exposed	3 / 4 (75.00%)	4 / 6 (66.67%)	5 / 9 (55.56%)
occurrences (all)	3	4	5
Constipation			
subjects affected / exposed	2 / 4 (50.00%)	4 / 6 (66.67%)	5 / 9 (55.56%)
occurrences (all)	2	4	5
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	4 / 6 (66.67%)	4 / 9 (44.44%)
occurrences (all)	1	4	4
Dyspepsia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Oesophagitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Other			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 4 (25.00%)	4 / 6 (66.67%)	7 / 9 (77.78%)
occurrences (all)	1	4	7
Haematuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Back pain			
subjects affected / exposed	2 / 4 (50.00%)	2 / 6 (33.33%)	2 / 9 (22.22%)
occurrences (all)	2	2	2
Soft tissue necrosis lower			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Other			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Mucosal infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Skin infection			

subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Upper respiratory infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	4 / 9 (44.44%)
occurrences (all)	0	2	4
Metabolism and nutrition disorders			
anorexia			
subjects affected / exposed	1 / 4 (25.00%)	3 / 6 (50.00%)	2 / 9 (22.22%)
occurrences (all)	1	3	2
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Hypernatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 6 (33.33%)	8 / 9 (88.89%)
occurrences (all)	2	2	8
Hypocalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	4 / 9 (44.44%)
occurrences (all)	1	2	4
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	4 / 9 (44.44%)
occurrences (all)	0	1	4
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Hyponatraemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	4 / 9 (44.44%)
occurrences (all)	1	2	4

Hypophosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	4 / 9 (44.44%)
occurrences (all)	1	1	4

Non-serious adverse events	AZD4547, Gemcitabine + Cisplatin	Gemcitabine + Cisplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Phlebitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Thromboembolic event			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Oedema limbs			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	3 / 5 (60.00%)	5 / 5 (100.00%)	
occurrences (all)	3	5	
Fever			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

Non-cardiac chest pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Testicular pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hoarseness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Confusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

Depression			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 5 (80.00%)	4 / 5 (80.00%)	
occurrences (all)	4	4	
Alkaline phosphatase increased			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
GGT increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 5 (60.00%)	
occurrences (all)	0	3	
Other			
subjects affected / exposed	3 / 5 (60.00%)	4 / 5 (80.00%)	
occurrences (all)	3	15	
Platelet count decreased			
subjects affected / exposed	2 / 5 (40.00%)	5 / 5 (100.00%)	
occurrences (all)	2	5	
Weight loss			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			
subjects affected / exposed	3 / 5 (60.00%)	5 / 5 (100.00%)	
occurrences (all)	3	5	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Sinus tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Aphonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Dysgeusia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Other			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Olfactory nerve disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Stroke			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 5 (80.00%)	5 / 5 (100.00%)	
occurrences (all)	4	5	
Leukocytosis			

subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Other			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hearing impaired			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Eye disorders			
Blurred vision			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Other			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Glaucoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Retinal detachment			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Watering eyes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Cheilitis			

subjects affected / exposed	3 / 5 (60.00%)	1 / 5 (20.00%)	
occurrences (all)	3	1	
Constipation			
subjects affected / exposed	3 / 5 (60.00%)	2 / 5 (40.00%)	
occurrences (all)	3	2	
Diarrhoea			
subjects affected / exposed	3 / 5 (60.00%)	1 / 5 (20.00%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Oesophagitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	3 / 5 (60.00%)	
occurrences (all)	0	3	
Other			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Ileus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	4 / 5 (80.00%)	4 / 5 (80.00%)	
occurrences (all)	4	4	
Periodontal disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Vomiting			

subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Dry skin			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Nail loss			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Pruritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Other			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Skin hyperpigmentation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 5 (100.00%)	2 / 5 (40.00%)	
occurrences (all)	5	2	
Haematuria			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Urinary retention			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Soft tissue necrosis lower			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Infections and infestations			
Other			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Mucosal infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Upper respiratory infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	4 / 5 (80.00%)	3 / 5 (60.00%)	
occurrences (all)	4	3	
Metabolism and nutrition disorders			
anorexia			
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	
occurrences (all)	1	3	
Dehydration			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	
occurrences (all)	0	0	
Hypercalcaemia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Hypernatraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2012	Protocol v2
21 November 2012	Protocol v3
15 February 2013	Protocol v4
12 February 2014	Protocol v5
18 May 2015	Protocol v6

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Recruitment to the trial was slower than expected so the sample size for the randomised expansion phase was not reached. The number of patients included in this analysis is therefore lower than desired.

Notes: