Clinical trial results:
A phase I/II study of first line Ganetespib with pemetrexed/cisplatin, in patients with malignant pleural mesothelioma

Summary

EudraCT number	2012-001598-10
Trial protocol	GB
Global end of trial date	17 December 2018

Results information

Result version number	v1 (current)
This version publication date	20 November 2020
First version publication date	20 November 2020

Trial information

Trial identification

Sponsor protocol code	UCL/12/0158

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01590160
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Meso-02 Trial Co-ordinator, CR UK & UCL Cancer Trials Centre,, University College London, +44 207679891, ctc.sponsor@ucl.ac.uk
Scientific contact	Meso-02 Trial Co-ordinator, CR UK & UCL Cancer Trials Centre,, University College London, +44 2076799891, ctc.sponsor@ucl.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	04 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2018
Global end of trial reached?	Yes
Global end of trial date	17 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question for the phase I study is to find the maximum tolerated dose of Ganetespib, and use this information with the number of chemotherapy cycles administered to determine the most appropriate dose of Ganetespib for the phase II trial. For the phase II study, the principle research question is to determine whether adding Ganetespib to pemetrexed and cisplatin using the dose from the Phase I part of the study, versus pemetrexed and cisplatin chemotherapy improves progression free survival (first disease progression or death of any cause).

Protection of trial subjects:

Regular Trial Management Group meetings and Independent Data Monitoring Committee meetings were held throughout the trial to monitor overall safety in the patient group. Pharmacovigilance requirements and safety compliance rules were detailed in the trial protocol with overall risk assessment, on-site monitoring and central monitoring conducted by the trial teams.
Patient data is stored in a secure manner and the trial is registered in accordance with the Data Protection Act.

Background therapy:

Intravenous pemetrexed (500mg/m2) with vitamin B12/folate supplementation was administered on day 1 of each 21-day cycle to all patients regardless of platinum therapy and ganetespib dose.

Evidence for comparator:

No comparators were used in this study.

Actual start date of recruitment	01 April 2013
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: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

27 patients were recruited between 4th September 2013 and 10th November 2015.
Patients were recruited from 4 different UK NHS hospital sites

Pre-assignment

Screening details:

Patients enrolled were chemo-naïve with a confirmed diagnosis of malignant pleural mesothelioma.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cisplatin

Arm description:

Patients were given a one-hour intravenous ganetespib infusion on days 1 and 15 of each 21-day cycle, at one of three dose levels: 100 mg/m2, 150 mg/m2, or 200 mg/m2. Patients also received a 10-minute intravenous pemetrexed infusion of 500 mg/m2 (with vitamin B12 and folate supplementation) immediately after ganetespib infusion on day 1 only. Additionally received cisplatin (75 mg/m2 intravenously over 2 hours) 30 minutes after the completion of pemetrexed infusion.

Arm type	Experimental
Investigational medicinal product name	Ganetespib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose-escalation of ganetespib was conducted using the 3+3 design with a starting dose of 100 mg/m2.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin was given at as an intravenous infusion at a dose of 75mg/m2 infused over 2 hours on day 1 every 21 days during the treatment.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 500mg/m2 IV on day 1 every 21 days during the treatment.

Arm title	Carboplatin

Arm description:

For patients receiving carboplatin with ganetespib and pemetrexed (i.e. the ‘carboplatin cohort’), dose-

escalation of ganetespib was conducted using an accelerated titration design with a starting dose of 100 mg/m2. At dose levels below 200 mg/m2, one patient would receive treatment; if no DLT was observed, the next patient would receive the next highest dose; otherwise, a 3+3 design would begin (i.e. the same as for the cisplatin-treated cohort). If ganetespib reached the estimate of the MTD, the cohort was expanded to 9 patients overall.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was given an intravenous infusion at a dose of AUC5 infused over 30 minutes on day 1 every 21 days during the treatment.

Investigational medicinal product name	Ganetespib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose-escalation of ganetespib was conducted using an accelerated titration design with a starting dose of 100 mg/m2.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 500mg/m2 IV on day 1 every 21 days during the treatment.

Number of subjects in period 1	Cisplatin	Carboplatin
Started	16	11
Completed	16	11

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	8	
From 65-84 years	19	19	
85 years and over	0	0	
Age continuous			
Age at study registration.			
Units: years			
median	66		
full range (min-max)	37 to 76	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	25	25	
Histology Units: Subjects			
Epithelioid	21	21	
Non-epithelioid	6	6	
ECOG performance status			
Eastern Cooperative Oncology Group (ECOG)			
Units: Subjects			
ECOG 0	6	6	
ECOG 1	21	21	
EORTC Prognostic Score			
European Organisation for Research and Treatment of Cancer (EORTC)			
Units: Subjects			
Good	2	2	
Poor	25	25	
Platinum Treatment Units: Subjects			
Cisplatin	16	16	
Carboplatin	11	11	
Ganetespib dose (mg/m2)			

Units: Subjects			
100 (Cisplatin arm)	4	4	
100 (Carboplatin arm)	1	1	
150 (Cisplatin arm)	3	3	
150 (Carboplatin arm)	1	1	
200 (Cisplatin arm)	9	9	
200 (Carboplatin arm)	9	9	

Subject analysis sets

Subject analysis set title	100 mg/m2 Dose Level
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients treated with 100mg/m2 ganetespib dose.	
Subject analysis set title	150 mg/m2 Dose Level
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients treated with 150 mg/m2 ganetespib dose.	
Subject analysis set title	200 mg/m2 Dose Level
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients treated with 200 mg/m2 ganetespib dose.	

Reporting group values	100 mg/m2 Dose Level	150 mg/m2 Dose Level	200 mg/m2 Dose Level
Number of subjects	5	4	18
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)	1	1	6
From 65-84 years	4	3	12
85 years and over	0	0	0
Age continuous			
Age at study registration.			
Units: years			
median	68	65	67.5
full range (min-max)	59 to 73	63 to 66	37 to 76
Gender categorical Units: Subjects			
Female	0	0	2
Male	5	4	16
Histology Units: Subjects			
Epithelioid	2	2	17
Non-epithelioid	3	2	1

ECOG performance status			
Eastern Cooperative Oncology Group (ECOG)			
Units: Subjects			
ECOG 0	1	1	4
ECOG 1	4	3	14
EORTC Prognostic Score			
European Organisation for Research and Treatment of Cancer (EORTC)			
Units: Subjects			
Good	0	0	2
Poor	5	4	16
Platinum Treatment Units: Subjects			
Cisplatin	4	3	9
Carboplatin	1	1	9
Ganetespib dose (mg/m2) Units: Subjects			
100 (Cisplatin arm)	4	0	0
100 (Carboplatin arm)	1	0	0
150 (Cisplatin arm)	0	3	0
150 (Carboplatin arm)	0	1	0
200 (Cisplatin arm)	0	0	9
200 (Carboplatin arm)	0	0	9

End points

End points reporting groups

Reporting group title	Cisplatin

Reporting group description:

Patients were given a one-hour intravenous ganetespib infusion on days 1 and 15 of each 21-day cycle, at one of three dose levels: 100 mg/m2, 150 mg/m2, or 200 mg/m2. Patients also received a 10-minute intravenous pemetrexed infusion of 500 mg/m2 (with vitamin B12 and folate supplementation) immediately after ganetespib infusion on day 1 only. Additionally received cisplatin (75 mg/m2 intravenously over 2 hours) 30 minutes after the completion of pemetrexed infusion.

Reporting group title	Carboplatin

Reporting group description:

For patients receiving carboplatin with ganetespib and pemetrexed (i.e. the 'carboplatin cohort'), dose-escalation of ganetespib was conducted using an accelerated titration design with a starting dose of 100 mg/m2. At dose levels below 200 mg/m2, one patient would receive treatment; if no DLT was observed, the next patient would receive the next highest dose; otherwise, a 3+3 design would begin (i.e. the same as for the cisplatin-treated cohort). If ganetespib reached the estimate of the MTD, the cohort was expanded to 9 patients overall.

Subject analysis set title	100 mg/m2 Dose Level
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients treated with 100mg/m2 ganetespib dose.

Subject analysis set title	150 mg/m2 Dose Level
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients treated with 150 mg/m2 ganetespib dose.

Subject analysis set title	200 mg/m2 Dose Level
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients treated with 200 mg/m2 ganetespib dose.

Primary: Dose-limiting toxicities during cycle 1 and 2

End point title	Dose-limiting toxicities during cycle 1 and 2[1]

End point description:

Toxicities were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0). A DLT was defined as any of the following adverse events deemed definitely, probably, or possibly related to ganetespib therapy: grade 3 or 4 non-hematologic events except diarrhoea, nausea and vomiting lasting more than 48 hours despite maximum medical therapy; grade 4 thrombocytopenia or neutropenia lasting longer than 7 days; febrile neutropenia, any drug-related adverse event leading to an interruption of ganetespib for longer than 14 days; or any clinically significant toxicity leading to dose reduction for ganetespib.

End point type	Primary

End point timeframe:

DLT assessment applied to cycles 1 and 2 only for patients in the cisplatin cohort, and cycle 1 only for the carboplatin cohort

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: Dose Limiting Toxicities (DLTs) observed in each platinum therapy arm and per dose level are reported as per CTCAE v4.0 and the study definition of DLT. Therefore, no statistical analyses or null hypothesis significance testing are required in identifying DLTs. We report the number of DLTs per platinum therapy arm, with details of the relevant event given as comments.

End point values	Cisplatin	Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[2]	11[3]		
Units: Dose Limiting Toxicities				
number (not applicable)	1	2		

Notes:

[2] - 200mg/m2 dose; grade 3 toxicity comprising nausea lasting >48 hours

[3] - 200mg/m2 dose (grade 2 infusion-related reaction; grade 3 nausea)

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Tolerated Dose

End point title	Maximum Tolerated Dose[4]

End point description:

Dose units are mg/m2.

End point type	Primary

End point timeframe:

Maximum Tolerated Dose was determined based on occurrences of Dose Limiting Toxicity during cycles 1 and 2 (cycle 1 for carboplatin only).

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: Maximum Tolerated Dose (MTD) is the dose agreed by the Trial Management Group to be maximally tolerable and based on the number of Dose Limiting Toxicities observed in each platinum therapy arm and per dose level. Therefore, no statistical analyses or null hypothesis significance testing are required in its identification.

End point values	Cisplatin	Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: Dose				
number (not applicable)	200	200		

Statistical analyses

No statistical analyses for this end point

Secondary: Best response

End point title	Best response

End point description:

Number of patients who achieve specific categories of response as their best response (defined by meso-modified RECIST v1.0).

End point type	Secondary

End point timeframe:

Median observed follow-up time for all patients was 10.7 months (range 2.3-49.4). Median follow-up time was 12.3 months (range 3.6-49.4) in the cisplatin cohort, and was 8 months (2.3-20.8) in the carboplatin cohort.

End point values	Cisplatin	Carboplatin	100 mg/m2 Dose Level	150 mg/m2 Dose Level
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15[5]	8[6]	4[7]	4
Units: Response				
Progressive Disease	1	0	0	1
Stable Disease	6	2	3	0
Partial Response	8	6	1	3
Complete Response	0	0	0	0

Notes:

[5] - 1 patient not evaluable for response

[6] - 3 patients not evaluable for response

[7] - 1 patient not evaluable for response

End point values	200 mg/m2 Dose Level			
Subject group type	Subject analysis set			
Number of subjects analysed	15[8]			
Units: Response				
Progressive Disease	0			
Stable Disease	5			
Partial Response	10			
Complete Response	0			

Notes:

[8] - 3 patients not evaluable for response

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Upper limit of 95% confidence interval = 99999999 implies limit not estimable

End point type	Secondary

End point timeframe:

Median observed follow-up time for all patients was 10.7 months (range 2.3–49.4). Median follow-up time was 12.3 months (range 3.6-49.4).

End point values	Cisplatin	Carboplatin	100 mg/m2 Dose Level	150 mg/m2 Dose Level
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	16	11	5[9]	4[10]
Units: months				
median (confidence interval 95%)	5.8 (4 to 10)	5.8 (4.2 to 11.3)	4.3 (2.8 to 99999999)	5.8 (1.2 to 99999999)

Notes:

[9] - No upper bound for 95% confidence interval

[10] - No upper bound for 95% confidence interval

End point values	200 mg/m2 Dose Level			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: months				
median (confidence interval 95%)	6.3 (5.0 to 10.0)			

Attachments (see zip file)	Progression-free survival by platinum treatment/MESO-02 - Progression-free survival by ganetespib dose/MESO-02 -

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Upper limit of 95% confidence interval = 99999999 implies limit not estimable

End point type	Secondary

End point timeframe:

Median observed follow-up time for all patients was 10.7 months (range 2.3–49.4). Median follow-up time was 12.3 months (range 3.6-49.4).

End point values	Cisplatin	Carboplatin	100 mg/m2 Dose Level	150 mg/m2 Dose Level
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	16	11	5[11]	4[12]
Units: months				
median (confidence interval 95%)	14.4 (6.3 to 28.7)	10.6 (6.3 to 19.5)	4.7 (3.6 to 99999999)	10.7 (8.8 to 99999999)

Notes:

[11] - No upper limit for 95% confidence interval

[12] - No upper limit for 95% confidence interval

End point values	200 mg/m2 Dose Level			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: months				
median (confidence interval 95%)	16.2 (8.0 to 21.7)			

Attachments (see zip file)	Overall survival by platinum treatment/MESO-02 - OS_graph. Overall survival by ganetespib dose/MESO-02 -

Statistical analyses

No statistical analyses for this end point

Secondary: Total Somatic Copy Number Alterations

End point title	Total Somatic Copy Number Alterations

End point description:

SCNA = number of somatic changes to chromosome structure that lead to gain or loss in copies of sections of DNA

End point type	Secondary

End point timeframe:

Median observed follow-up time for all patients was 10.7 months (range 2.3–49.4). Median follow-up time was 12.3 months (range 3.6-49.4).

End point values	Cisplatin	Carboplatin	100 mg/m2 Dose Level	150 mg/m2 Dose Level
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5[13]	6[14]	3[15]	0[16]
Units: alterations				
arithmetic mean (standard deviation)	85.8 (± 83.7)	98.7 (± 53.7)	72 (± 34)	()

Notes:

[13] - 11 patients had non-viable samples

[14] - 5 patients had non-viable samples

[15] - 2 patients had non-viable samples

[16] - 4 patients had non-viable samples

End point values	200 mg/m2 Dose Level			
Subject group type	Subject analysis set			
Number of subjects analysed	8[17]			
Units: alterations				
arithmetic mean (standard deviation)	100.6 (± 74.5)			

Notes:

[17] - 10 patients had non-viable samples

Statistical analyses

Statistical analysis title	Correlation with best total tumor burden reduction
Comparison groups	Cisplatin v Carboplatin

Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.879
Method	Spearman correlation
Parameter estimate	Spearman correlation
Point estimate	0.0714
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.782

Notes:

[18] - Spearman correlation of best reduction in total tumor burden and total SCNA

Statistical analysis title	Association with time to progression

Statistical analysis description:

Cox regression of time to progression on total SCNA

Comparison groups	Cisplatin v Carboplatin
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.295
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.02

Secondary: Total Loss of Heterozygosity

End point title	Total Loss of Heterozygosity

End point description:

LOH = the number of somatic cells containing only one copy of an allele

End point type	Secondary

End point timeframe:

Median observed follow-up time for all patients was 10.7 months (range 2.3–49.4). Median follow-up time was 12.3 months (range 3.6-49.4).

End point values	Cisplatin	Carboplatin	100 mg/m2 Dose Level	150 mg/m2 Dose Level
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5[19]	6[20]	3[21]	0[22]
Units: alterations				
arithmetic mean (standard deviation)	23.4 (± 17.7)	21.7 (± 10.4)	31.3 (± 18.8)	()

Notes:

[19] - 11 patients had non-viable samples

[20] - 5 patients had non-viable samples

[21] - 2 patients had non-viable samples

[22] - 4 patients had non-viable samples

End point values	200 mg/m2 Dose Level			
Subject group type	Subject analysis set			
Number of subjects analysed	8[23]			
Units: alterations				
arithmetic mean (standard deviation)	19.1 (± 10.5)			

Notes:

[23] - 10 patients had non-viable samples

Statistical analyses

Statistical analysis title	Correlation with best total tumor burden reduction
Comparison groups	Cisplatin v Carboplatin
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.0782
Method	Spearman correlation
Parameter estimate	Spearman correlation
Point estimate	-0.703
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.952
upper limit	0.107

Notes:

[24] - Spearman correlation of best reduction in total tumor burden with total LOH

Statistical analysis title	Association of LOH with time to progression
Statistical analysis description: Cox regression of time to progression on total LOH	
Comparison groups	Cisplatin v Carboplatin
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.24

Secondary: Total homozygous deletions

End point title	Total homozygous deletions

End point description:

Total homozygous deletions = total number of biallelic copy number losses

End point type	Secondary

End point timeframe:

Median observed follow-up time for all patients was 10.7 months (range 2.3–49.4). Median follow-up time was 12.3 months (range 3.6-49.4).

End point values	Cisplatin	Carboplatin	100 mg/m2 Dose Level	150 mg/m2 Dose Level
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	5[25]	6[26]	3[27]	0[28]
Units: deletions				
arithmetic mean (standard deviation)	2.4 (± 2.8)	3.5 (± 3.3)	3.7 (± 3.5)	()

Notes:

[25] - 11 patients had non-viable samples

[26] - 5 patients had non-viable samples

[27] - 2 patients had non-viable samples

[28] - 4 patients had non-viable samples

End point values	200 mg/m2 Dose Level			
Subject group type	Subject analysis set			
Number of subjects analysed	8[29]			
Units: deletions				
arithmetic mean (standard deviation)	2.8 (± 3.0)			

Notes:

[29] - 10 patients had non-viable samples

Statistical analyses

Statistical analysis title	Correlation with best total tumor burden reduction

Statistical analysis description:

Correlation of best reduction in total tumor burden with total homozygous deletions

Comparison groups	Cisplatin v Carboplatin

Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.908
Method	Spearman correlation
Parameter estimate	Spearman correlation
Point estimate	-0.0541
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.776
upper limit	0.729

Statistical analysis title	Association with time to progression
Statistical analysis description:	
Cox regression of time to progression on total homozygous deletions	
Comparison groups	Cisplatin v Carboplatin
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.201
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.73

Secondary: Number of cycles of platinum and pemetrexed given

End point title	Number of cycles of platinum and pemetrexed given
End point description:	
Number of cycles for which trial treatment was given to patients per platinum arm.	
End point type	Secondary
End point timeframe:	
Number of cycles of trial treatment given was from first treatment administration to a maximum of 6 planned treatment cycles.	

End point values	Cisplatin	Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: Cycles				
median (full range (min-max))	4 (1 to 6)	3 (1 to 5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred between informed consent and up to 30 days after administration of the last dose of trial treatment

Adverse event reporting additional description:

For each type of adverse event, the maximum toxicity grade was obtained for each patient.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Cisplatin

Reporting group description:

Patients were given a one-hour intravenous ganetespib infusion on days 1 and 15 of each 21-day cycle, at one of three dose levels: 100 mg/m2, 150 mg/m2, or 200 mg/m2. Patients also received a 10-minute intravenous pemetrexed infusion of 500 mg/m2 (with vitamin B12 and folate supplementation) immediately after ganetespib infusion on day 1 only. Additionally received cisplatin (75 mg/m2 intravenously over 2 hours) 30 minutes after the completion of pemetrexed infusion.

Reporting group title	Carboplatin

Reporting group description:

For patients receiving carboplatin with ganetespib and pemetrexed (i.e. the 'carboplatin cohort'), dose-escalation of ganetespib was conducted using an accelerated titration design with a starting dose of 100 mg/m2. At dose levels below 200 mg/m2, one patient would receive treatment; if no DLT was observed, the next patient would receive the next highest dose; otherwise, a 3+3 design would begin (i.e. the same as for the cisplatin-treated cohort). If ganetespib reached the estimate of the MTD, the cohort was expanded to 9 patients overall.

Serious adverse events	Cisplatin	Carboplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 16 (68.75%)	9 / 11 (81.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	4 / 16 (25.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 16 (37.50%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 16 (25.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chest wall pain			

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection - Other (chest)	Additional description: Other (non CTCAE)		
alternative dictionary used: MedDRA 23			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (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, specify			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection			
subjects affected / exposed	1 / 16 (6.25%)	4 / 11 (36.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalemia			

subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cisplatin	Carboplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	11 / 11 (100.00%)	
Vascular disorders			
Hot flashes			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Flushing			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Phlebitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vasculitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	15 / 16 (93.75%)	5 / 11 (45.45%)	
occurrences (all)	34	11	
Flu like symptoms			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Non-cardiac chest pain			
subjects affected / exposed	5 / 16 (31.25%)	3 / 11 (27.27%)	
occurrences (all)	8	4	
Infusion related reaction			
subjects affected / exposed	0 / 16 (0.00%)	3 / 11 (27.27%)	
occurrences (all)	0	3	
Chills			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infusion site extravasation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	5 / 16 (31.25%)	0 / 11 (0.00%)	
occurrences (all)	6	0	
General disorders and administration site conditions - Other, (Intermittent hot and cold)			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 16 (43.75%)	2 / 11 (18.18%)	
occurrences (all)	15	2	
Dyspnea			
subjects affected / exposed	10 / 16 (62.50%)	6 / 11 (54.55%)	
occurrences (all)	15	6	
Epistaxis			
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	10	1	
Pleural effusion			

subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Allergic rhinitis			
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Apnea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Sleep apnea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Sore throat			
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders - Other, specify	Additional description: Haemoptysis		
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
Insomnia			
subjects affected / exposed	3 / 16 (18.75%)	3 / 11 (27.27%)	
occurrences (all)	6	4	
Mania			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Alkaline phosphatase increased			

subjects affected / exposed	3 / 16 (18.75%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Neutrophil count decreased			
subjects affected / exposed	4 / 16 (25.00%)	2 / 11 (18.18%)	
occurrences (all)	7	4	
Platelet count decreased			
subjects affected / exposed	1 / 16 (6.25%)	3 / 11 (27.27%)	
occurrences (all)	3	4	
weight loss			
subjects affected / exposed	6 / 16 (37.50%)	2 / 11 (18.18%)	
occurrences (all)	6	2	
Creatinine increased			
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Weight gain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Investigations - Other, specify	Additional description: Increased platelets		
subjects affected / exposed	0 / 16 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Chest pain - cardiac			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders - Other, specify	Additional description: Intermittent palpitations		

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Lethargy			
subjects affected / exposed	3 / 16 (18.75%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 16 (25.00%)	1 / 11 (9.09%)	
occurrences (all)	7	1	
Syncope			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	6	0	
Dysgeusia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Paresthesia			
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Tremor			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders - Other, specify	Additional description: Taste disturbance		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	14 / 16 (87.50%)	5 / 11 (45.45%)	
occurrences (all)	41	15	
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
Hearing impaired			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 16 (12.50%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
eye disorder-other			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Blurred vision			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	3	
Eye pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Glaucoma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Eye disorders - Other, specify	Additional description: Perioribital, haemorrhage eye		
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
abdominal pain			
subjects affected / exposed	6 / 16 (37.50%)	3 / 11 (27.27%)	
occurrences (all)	22	3	
Constipation			
subjects affected / exposed	9 / 16 (56.25%)	3 / 11 (27.27%)	
occurrences (all)	27	5	
Diarrhea			
subjects affected / exposed	8 / 16 (50.00%)	7 / 11 (63.64%)	
occurrences (all)	83	10	
Dry mouth			

subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
General disorders and administration site conditions - Other			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	12 / 16 (75.00%)	6 / 11 (54.55%)	
occurrences (all)	46	14	
Oral pain			
subjects affected / exposed	1 / 16 (6.25%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	10 / 16 (62.50%)	1 / 11 (9.09%)	
occurrences (all)	30	5	
Ascites			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Rectal hemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	5 / 16 (31.25%)	0 / 11 (0.00%)	
occurrences (all)	8	0	
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hemorrhoids			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

Mucositis oral			
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	3 / 16 (18.75%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)	2 / 11 (18.18%)	
occurrences (all)	9	2	
Hyperhidrosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	3	0	
Dry skin			
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Rash acneiform			
subjects affected / exposed	3 / 16 (18.75%)	0 / 11 (0.00%)	
occurrences (all)	7	0	
Skin and subcutaneous tissue disorders - Other, specify	Additional description: Night sweats		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders - Other, specify	Additional description: Difficulty in micturition		
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			

Back Pain			
subjects affected / exposed	5 / 16 (31.25%)	2 / 11 (18.18%)	
occurrences (all)	7	2	
Hypokalemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	2	
Buttock pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Chest wall pain			
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)	2 / 11 (18.18%)	
occurrences (all)	5	2	
Pain in extremity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Infections and infestations - Other			
subjects affected / exposed	1 / 16 (6.25%)	3 / 11 (27.27%)	
occurrences (all)	1	4	
Lung infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	3	2	
Upper respiratory infection			
subjects affected / exposed	5 / 16 (31.25%)	1 / 11 (9.09%)	
occurrences (all)	5	1	
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	2	4	
Wound infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Papulopustular rash			

subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	7 / 16 (43.75%)	4 / 11 (36.36%)	
occurrences (all)	16	11	
Hyperkalemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Hypermagnesemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Hypomagnesemia			
subjects affected / exposed	0 / 16 (0.00%)	4 / 11 (36.36%)	
occurrences (all)	0	5	
Hypercalcemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Hyperglycemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 11 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2013	• Section 2.1 (ganetespib) – updated in line with v8.0 of the IB: no. of patients being treated with ganetespib and the number of new studies. Adverse Events has also been updated with new events and the percentages reported has now changed as the sample size increased. • Section 4.1 updated e – sites must assess a patient's ability to understand verbal explanations and written information in English. If local interpreters are not available and fully informed consent is not deemed possible, the patient should not be considered for the trial • Section 7.3.1 – updated in line with v8.0 of the IB: (Events of special interest), updated instructions for investigators regarding neutropenia. • Section 7.5 – Ganetespib administration – 'D5W' American terminology changed to '5% Glucose' to concentration of solution when making infusion. • Section 7.14.1 – Management of severe or complicated neutropenia – recommendation of GCSF prophylactic use during subsequent treatment cycles in cases of Neutropenia lasting more than 7 days • Section 7.14.2 - Ganetespib pre-medication and management of hypersensitivity reactions – minor edits in line with IB: upon recover patients may also or re-schedule patient for re-treatment • Section 9.0 updated – data in CRFs should be verifiable by source date • Section 9.1 and 9.4 – instruction regarding CRF corrections and update regarding the use of query sheets • Section 10.0 updated in line with CTC template: UCL CTC will consider events evaluated as possibly, probably or definitely related to be adverse reactions • Section 10.0 updated - 'Exemptions from SAE Report Submission' updated to include events that occur after 30 days post last trial treatment administration that are not considered to be side-effects of the trial treatment and are not AEs of special interest. • Section 12.2 updated – Central Monitoring – Data received at UCL CTC will be subject to review in accordance with section 9

14 May 2013	•Updated with Clinicaltrials.gov number •Section 1.1 & 5.4– Units for Haemoglobin changed from g/dL to g/L in accordance with the new national units •Section 1.2 – Trial Schema – Mosteller formula for calculation of BSA changed to Dubois and Dubois •Section 4.0 – Sites must assess a patient's ability to understand verbal and written information in English •Section 5.3 – Patient Eligibility -Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). •Section 7.3 – Phase I trial - Mosteller formula for calculation of BSA changed to Dubois and Dubois. Randomised Phase II trial - Mosteller formula for calculation of BSA changed to Dubois and Dubois •Section 7.5 - Ganetespib infusion now supplied in 2 different vials sizes; 300mg and 400mg. Container and Storage conditions added for 300mg vial. •Section 7.5 - The DuBois and DuBois formula is the recommended method to be used for the calculation of BSA. •Section 7.11.1 – Ganetespib dose reductions – ANC values for Haematological Toxicity clarified •Section 7.11.3 - The dose modification schedules should be followed as closely as possible but clinical judgement should be used in individual cases. •Section 9 – Some data will be recorded directly on the CRFs and it will be considered to be the source document. •Section 12.1 – Key areas for assessment during on site monitoring removed altogether and referenced to the trial monitoring plan document. •Section 12.2 – Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). •Section 13 – Withdrawals – update to language •Section 16 – Ethical and Regulatory Approvals – updated in line with new CTC template. •Section 16.3 - updated in line with new CTC template - Site Approvals reference to Lead CLRN removed •Section 17.1 – Sponsor Details updated •Section 20 – Translational Research – Address for diagnostic tissue samples updated.
07 August 2013	• Change in Trial Coordinator's name • 7.3 – clarification loperamide is administered prior to day 1 and 15 ganetespib administration • 7.11 clarification the two dose reductions that can occur before a patient must be withdrawn refers to ganetespib only • 7.14.2 - chlorphenamine added as an alternative to diphenhydramine • 7.15 - correction to the telephone number for drug-specific advice for ganetespib, and alternative numbers added • 8.1, 8.2 & 8.3 – typographical errors amended • Appendix 2 – table corrected to match protocol

19 March 2014	•Change in title from cisplatin to platinum to reflect option of using carboplatin in phase II •Change in TMG members •Section 1.1 - Summary of trial design updated •Sections 1.2, 2.2, 7.3 - details added to include additional patients to be registered to receive ganetespib, pemetrexed and carboplatin in the phase I. This group will be recruited concurrently with the group of patients used to confirm the MTD. •Section 1.2.3, 2.2.2, 7.3.2. - updated to reflect the option of using carboplatin in the phase II •Section 2.1 – Clinical experience and Adverse Events updated in line with new version of IB for ganetespib •Sections 2.2.3, 8.1, 8.3, 8.4, 20 and Appendix 2 – update to schedule of blood sample collection for translational research •Section 5.5 – Patient Exclusion criteria updated in line with version 9.0 of IB for ganetespib •Section 6.3 – updated to include carboplatin (to be supplied from hospital stock) •Section 7 – update to include carboplatin as IMP •Section 7.3.1 – updated to clarify definition of DLTs •Section 7.3.1 – updated to clarify accelerated titrated phase I design •Section 7.3.1, 7.15.1, 7.15.2, 7.15.3 – Management of events of special interest updated in line with version 9.0 of IB for ganetespib •Section 7.5 – ganetespib storage conditions updated •Section 7.12.1 – dose modifications for ganetespib •Section 7.13.2 drug interaction section updated for ganetespib in line with version 9.0 of IB •Section 7.14, 7.14.1 – Medications used with caution updated in line with version 9.0 of IB for ganetespib •Section 8.2, Appendices 2 and 3 – Schedule of ECG and dose modifications in the event of QTc prolongation updated in line with version 9.0 of IB for ganetespib •Section 15 – Statistical considerations updated to reflect the option of using carboplatin in phase II •Section 21 – references updated to incSynta studies •Appendix 5 – new appendix listing drugs with a risk of Torsades de Pointes
30 September 2015	• Change to Trial Coordinator • Update to exclusion criteria to reflect new safety data • Section 2.1 - Background clinical information and adverse effects for ganetespib have been updated to reflect new data. • Section 2.2.3 – Changes to translational blood sample evaluation and use of results affecting future sample analysis. • Section 7.3 – clarification – DLT assessments for the carboplatin arm will be made after 1 cycle • Section 7.3.1 – Update and additional information for ocular, liver and gastrointestinal perforation toxicities • Section 7.7 – Symptom review for cisplatin added prior to treatment • Section 7.12.3.7 – Information on use of local guidelines for dose reduction of carboplatin • Section 7.13.1 – Instructions on availability of equipment for anaphylaxis • Section 7.15.1 – New information for prophylactic use of Loperamide • Section 7.15.4 – addition of information for premedication regimen • Section 8.2 – change to required ANC value at Day 1 assessment and additional information explaining requirement to take Day 15 bloods. • Section 10.1 – Updated to reflect use of RSI in defining SUSARs • Section 15.4.2 – Additional information relating to interim analysis and timing of IDMC. • Appendix 5 – information relating to Torsades de pointes updated to reflect new data since last update • Appendix 6 – Additional appendix added to protocol outlining meso-modified criteria and what is required when reporting trial CT scans.

09 January 2017	• Change in trial statistician • Change in trial oversight • Change in trial coordinator • Change in drug company name from Synta Pharmaceuticals Corp to Madrigal Pharmaceuticals Inc. following reverse merger • Decision by not to proceed with continuing the phase II of the trial included in relevant sections of protocol as follows: 1.1 Summary of trial design; 1.2. Trial Schema; 2.2 Trial Design; 6.2 Randomisation to the phase II trial; 15.3 Safety Monitoring during the phase II trial; and 15.4.2 Randomised phase II trial • Section 2.1 – number of patients exposed to ganetespib updated in line with IB version 11, 13Nov2015 • Section 7.16 Out-of-hours drug advice contact numbers for ganetespib updated • Section 7.3 – loperamide guidance in line with IB v11 – to allow treatment to continue for up to 24 hours • Section 7.3 and 7.12.1 – Dose modifications and frequency of ECG recordings relating to QTc prolongation updated in line with IB v11 • Appendix 2 – Scheduling of CT assessments reworded to reflect that outlined in section 8.2 • Appendix 2 – Additional wording regarding the frequency of ECG assessments in case of QTc prolongation • Appendix 5 – updated in line with IB v11
26 October 2018	• Section 7.5 Drug company information updated to reflect change in IMP sourcing information for gantespib • Sections 8.1, 8.2 and 8.4 – additional information regarding the sharing of pseudo-anonymised CT scan images for selected trial participants • Section 9.2 – new section on Imaging • Section 16 – updated in line with General Data Protection Regulation (GDPR) 2018 and Data Protection Legislation 2018 • Sections 1.1 and 14.1 - End of trial definition updated • New reference added for modified RECIST 1.1

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported