Clinical trial results:
A RANDOMIZED, PHASE 3 STUDY OF GANETESPIB IN COMBINATION WITH DOCETAXEL VERSUS DOCETAXEL ALONE IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG ADENOCARCINOMA

Summary

EudraCT number	2012-004349-34
Trial protocol	HU GB DE CZ BE ES PL SI AT NL IT
Global end of trial date	02 December 2015

Results information

Result version number	v1 (current)
This version publication date	24 March 2016
First version publication date	24 March 2016

Trial information

Trial identification

Sponsor protocol code	9090-14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01798485
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Synta Pharmaceuticals Corp.
Sponsor organisation address	45 Hartwell Avenue, Lexington, MA , United States, 02421
Public contact	President, Chief Executive Officer , Synta Pharmaceuticals Corp., +1 781-541-7261,
Scientific contact	VP Clinical Research, Synta Pharmaceuticals Corp., +1 781-541-7156,

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	19 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Compare overall survival (OS) in non-small-cell lung cancer (NSCLC) patients with adenocarcinoma histology treated with ganetespib in combination with docetaxel versus docetaxel alone.

Protection of trial subjects:

All Investigators obtained Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approval for this protocol and written informed consent prior to study initiation in adherence with 21 Code of Federal Regulations (CFR) 50 and 21 CFR 56.

This trial was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Prior to the start of any protocol-specific evaluations or screening procedures, the Investigator (or designated staff) explained the nature of the study and its risks and benefits to the patient (or the patient's legal representative). Each patient received an informed consent document with patient information. Patients were to be given ample time to read the information and the opportunity to ask questions. Informed consent was required to be obtained from each patient prior to performing any protocol-specific evaluations.
One copy of the signed informed consent document was given to the patient, and another was retained by the Investigator.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	20 March 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	Netherlands: 10
Country: Number of subjects enrolled	Poland: 79
Country: Number of subjects enrolled	Slovenia: 7
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 53

Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 82
Country: Number of subjects enrolled	Bosnia and Herzegovina: 15
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Romania: 94
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	Serbia: 99
Country: Number of subjects enrolled	Ukraine: 43
Worldwide total number of subjects	696
EEA total number of subjects	420

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)	474
From 65 to 84 years	222
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

209 sites screened at least one patient and 175 sites randomized at least one patient.

Pre-assignment

Screening details:

1220 patients with advanced NSCLC of adenocarcinoma histology diagnosed ≥6 months prior to study entry were screened. 696 patients were randomized in a 1:1 ratio to two arms and stratified by:

- ECOG (0 versus 1)
- Screening total LDH levels (normal vs. elevated)
- Geographic region (North America and Western Europe vs. Rest of World)

Period 1

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

Blinding implementation details:

This study was open-label due to the inability to blind patients and investigative site staff to the distinct side effects of ganetespib, ie, diarrhea.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ganetespib and Docetaxel

Arm description:

Ganetespib (150 mg/m^2) and docetaxel (75 mg/m^2) were administered as separate 1-hour IV infusions on Day 1 of each 3-week treatment cycle. Administration of ganetespib preceded the administration of docetaxel. Ganetespib was administered again on Day 15 of each cycle.

Arm type	Experimental
Investigational medicinal product name	Ganetespib
Investigational medicinal product code	
Other name	STA-9090
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganetespib (150 mg/m^2) and docetaxel (75 mg/m^2) were administered as separate 1-hour IV infusions on Day 1 of each 3-week treatment cycle. Administration of ganetespib preceded the administration of docetaxel. Ganetespib was administered again on Day 15 of each cycle.
After docetaxel treatment ceased, participants whose disease has not progressed continued to receive ganetespib alone until disease progression, unacceptable toxicity, or patient's withdrawal of consent.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere, Docecad
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel (75 mg/m^2) was administered as a 1-hour IV infusion on Day 1 of each 3-week treatment cycle. Docetaxel was given after ganetespib in the experimental treatment arm.
Docetaxel, 75 mg/m^2, was administered according to prevailing practice and Investigator decision, generally until disease progression, intolerability, or patient's withdrawal of consent.

Arm title	Docetaxel

Arm description:

Docetaxel (75 mg/m^2) was administered on Day 1 of a 3-week treatment cycle by 1-hour IV infusion.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere, Docecad
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel (75 mg/m^2) was administered as a 1-hour IV infusion on Day 1 of each 3-week treatment cycle. Docetaxel was given after ganetespib in the experimental treatment arm.
Docetaxel, 75 mg/m^2, was administered according to prevailing practice and Investigator decision, generally until disease progression, intolerability, or patient's withdrawal of consent.

Number of subjects in period 1	Ganetespib and Docetaxel	Docetaxel
Started	347	349
Safety Population as of 23 Dec 2015	338	342
Randomized as of 19 October 2015	335	337
Completed	1	59
Not completed	346	290
Clinical progression	35	24
Consent withdrawn by subject	27	31
Physician decision	14	10
Objective disease progression	152	106
Adverse event, non-fatal	32	40
Death	25	22
Sponsor decision	61	54
Lost to follow-up	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Ganetespib and Docetaxel
Reporting group description:	
Ganetespib (150 mg/m^2) and docetaxel (75 mg/m^2) were administered as separate 1-hour IV infusions on Day 1 of each 3-week treatment cycle. Administration of ganetespib preceded the administration of docetaxel. Ganetespib was administered again on Day 15 of each cycle.	
Reporting group title	Docetaxel
Reporting group description:	
Docetaxel (75 mg/m^2) was administered on Day 1 of a 3-week treatment cycle by 1-hour IV infusion.	

Reporting group values	Ganetespib and Docetaxel	Docetaxel	Total
Number of subjects	347	349	696
Age categorical Units: Subjects			
<65 years	227	247	474
>=65 years	120	102	222
Age continuous Units: years			
arithmetic mean	60.9	60.1	
standard deviation	± 8.93	± 8.69	-
Gender categorical Units: Subjects			
Female	141	135	276
Male	206	214	420
Race Units: Subjects			
Asian	1	1	2
Black or African American	1	6	7
White	341	340	681
Unknown or Not Reported	4	2	6
Geographic region Units: Subjects			
North America	41	44	85
Western Europe	101	96	197
Rest of World	205	209	414
Smoking history Units: Subjects			
Never Smoked	62	62	124
Ever Smoked	282	284	566
Unknown	3	3	6
Stage at Initial Diagnosis Units: Subjects			
I/II	22	19	41
IIIA	18	18	36
IIIB	52	52	104
IV	254	258	512
Unknown	1	2	3

ECOG at Study Entry			
Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a participants' disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis.			
Units: Subjects			
0 = Fully Active	124	125	249
1 = Restrictive but Ambulatory	223	224	447
2 = Ambulatory Unable to Work	0	0	0
3 = Limited Self-care	0	0	0
4 = Completely Disabled	0	0	0
Lactate Dehydrogenase (LDH) at Study Entry Units: Subjects			
Normal	246	247	493
Elevated	101	102	203
Brain Metastasis Units: Subjects			
Yes	65	55	120
No	282	294	576
Bone Metastasis Units: Subjects			
Yes	115	100	215
No	232	249	481
Intra-Thoracic Metastasis only Units: Subjects			
Yes	95	120	215
No	252	229	481
Time from Advanced NCSLC Diagnosis to Consent Units: months			
arithmetic mean	11.54	11.76	
standard deviation	± 5.995	± 7.74	-

End points

End points reporting groups

Reporting group title	Ganetespib and Docetaxel
Reporting group description:	
Ganetespib (150 mg/m^2) and docetaxel (75 mg/m^2) were administered as separate 1-hour IV infusions on Day 1 of each 3-week treatment cycle. Administration of ganetespib preceded the administration of docetaxel. Ganetespib was administered again on Day 15 of each cycle.	
Reporting group title	Docetaxel
Reporting group description:	
Docetaxel (75 mg/m^2) was administered on Day 1 of a 3-week treatment cycle by 1-hour IV infusion.	

Primary: Overall Survival as of 19 October 2015

End point title	Overall Survival as of 19 October 2015
End point description:	
Overall survival (OS) was measured from the date of randomization to the date of death from any cause.	
End point type	Primary
End point timeframe:	
up to 36 months	

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335[1]	337[2]		
Units: months				
median (confidence interval 95%)	10.9 (9 to 12.3)	10.5 (8.6 to 12.2)		

Notes:

[1] - Randomized population

[2] - Randomized population

Statistical analyses

Statistical analysis title	OS - Primary study hypothesis
Statistical analysis description:	
Primary study hypothesis was tested at a 2-sided, 0.05 significance level using a stratified log-rank test.	
Comparison groups	Ganetespib and Docetaxel v Docetaxel
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3293 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.111

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.899
upper limit	1.372

Notes:

[3] - P-value was from stratified log-rank test (strata: screening LDH, screening ECOG and geographic region).

Statistical analysis title	OS - Futility analysis

Statistical analysis description:

Futility analysis for the first Interim Analysis which had a database cutoff of 19 October 2015. For the first interim analysis, if the lower limit of the 2-sided 99.5% confidence interval for the Hazard Ratio was greater than 0.75, then the study could be stopped for futility, based on Data Monitoring Committee (DMC) recommendation.
Hazard ratio and 99.5% CI were calculated using the stratified Cox Proportional Hazards model (strata: screening LDH, screening ECOG and geographic region).

Comparison groups	Ganetespib and Docetaxel v Docetaxel
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.111
Confidence interval	
level	Other: 99.5 %
sides	2-sided
lower limit	0.821
upper limit	1.503

Notes:

[4] - Futility

Secondary: Progression-free Survival (PFS) as of 19 October 2015

End point title	Progression-free Survival (PFS) as of 19 October 2015

End point description:

The progression-free interval is the interval from the date of randomization until tumor progression per modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1), clinical progression, or death from any cause in the absence of progressive disease, whichever occurs first. Data represents the investigator's assessment.
Progressive Disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335[5]	337[6]		
Units: months				
median (confidence interval 95%)	4.2 (3.8 to 4.4)	4.3 (3.6 to 5.6)		

Notes:

[5] - Randomized population

[6] - Randomized population

Statistical analyses

Statistical analysis title	PFS
Comparison groups	Ganetespib and Docetaxel v Docetaxel
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1186 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.961
upper limit	1.403

Notes:

[7] - Significance level of 0.05.

Secondary: Overall Survival (OS) In Participants With an Elevated Screening Lactate Dehydrogenase (eLDH) as of 19 October 2015

End point title	Overall Survival (OS) In Participants With an Elevated Screening Lactate Dehydrogenase (eLDH) as of 19 October 2015

End point description:

OS was measured from the date of randomization to the date of death from any cause. Elevated LDH includes values above the upper limit of normal.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[8]	98[9]		
Units: months				
median (confidence interval 95%)	7.1 (5.4 to 11)	9 (6.2 to 10.3)		

Notes:

[8] - Randomized participants with elevated LDH at screening

[9] - Randomized participants with elevated LDH at screening

Statistical analyses

Statistical analysis title	OS - Elevated Screening LDH Patients
Comparison groups	Ganetespib and Docetaxel v Docetaxel
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2506 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.232
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.865
upper limit	1.754

Notes:

[10] - Significance level of 0.05. P-value was from stratified log-rank test (strata: screening ECOG and geographic region).

Secondary: Objective Response Rate (ORR) as of 19 October 2015

End point title	Objective Response Rate (ORR) as of 19 October 2015

End point description:

Percentage of participants whose best overall response, as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST 1.1), was either a complete response (CR) or a partial response (PR).
CR was defined as the disappearance (or normalization) of all target lesions. PR was defined as at least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335[11]	337[12]		
Units: percentage of participants				
number (confidence interval 95%)	13.7 (10.2 to 17.9)	16 (12.3 to 20.4)		

Notes:

[11] - Randomized patients

[12] - Randomized patients

Statistical analyses

Statistical analysis title	Objective Response Rate
Comparison groups	Ganetespib and Docetaxel v Docetaxel
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448 [13]
Method	Fisher exact

Notes:

[13] - Significance level of 0.05.

Secondary: Disease Control Rate (DCR) as of 19 October 2015

End point title	Disease Control Rate (DCR) as of 19 October 2015

End point description:

Percentage of participants whose best overall response, as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST 1.1), was either a complete response (CR), a partial response (PR), or stable disease (SD).
CR was defined as the disappearance (or normalization) of all target lesions. PR was defined as at least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of diameters while on study. For participants with a best response of SD, duration of SD must be for at least 6 weeks or 12 weeks.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335[14]	337[15]		
Units: percentage of participants				
number (confidence interval 95%)				
>=6 weeks	64.5 (59.1 to 69.6)	60.8 (55.4 to 66.1)		
>=12 weeks	46 (40.5 to 51.5)	46.9 (41.5 to 52.4)		

Notes:

[14] - Randomized patients

[15] - Randomized patients

Statistical analyses

Statistical analysis title	DCR: >=6 weeks
Comparison groups	Ganetespib and Docetaxel v Docetaxel

Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.339 [16]
Method	Fisher exact

Notes:

[16] - Significance level of 0.05.

Statistical analysis title	DCR: >= 12 weeks
Comparison groups	Ganetespib and Docetaxel v Docetaxel
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.817 [17]
Method	Fisher exact
Parameter estimate	Cox proportional hazard

Notes:

[17] - Significance level of 0.05.

Secondary: Kaplan-Meier Estimate of Duration of Response (DOR) as of 19 October 2015

End point title	Kaplan-Meier Estimate of Duration of Response (DOR) as of 19 October 2015

End point description:

Only participants who achieved a confirmed response (complete response (CR) or partial response (PR)) were included in the DOR analysis.
CR was defined as the disappearance (or normalization) of all target lesions.
PR was defined as at least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[18]	54[19]		
Units: months				
median (confidence interval 95%)	5.8 (3 to 5.9)	5.8 (4.3 to 6.9)		

Notes:

[18] - Randomized participants who had a confirmed response

[19] - Randomized participants who had a confirmed response

Statistical analyses

Statistical analysis title	DOR
Comparison groups	Ganetespib and Docetaxel v Docetaxel

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0111 [20]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.344
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.207
upper limit	4.551

Notes:

[20] - P-value was from stratified log-rank test (strata: screening LDH, screening ECOG and geographic region).

Secondary: Progression Free Survival (PFS) in Participants With an Elevated Screening Lactate Dehydrogenase (eLDH) as of 19 October 2015

End point title	Progression Free Survival (PFS) in Participants With an Elevated Screening Lactate Dehydrogenase (eLDH) as of 19 October 2015

End point description:

The progression-free interval is the interval from the date of randomization until tumor progression per modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1), clinical progression, or death from any cause in the absence of progressive disease, whichever occurs first. Data represents the investigator's assessment.
Progressive Disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Elevated LDH includes values above the upper limit of normal.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[21]	98[22]		
Units: months				
median (confidence interval 95%)	3 (2.4 to 4)	2.8 (2.2 to 4.1)		

Notes:

[21] - Randomized participants who had an elevated screening LDH

[22] - Randomized participants who had an elevated screening LDH

Statistical analyses

Statistical analysis title	PFS- eLDH

Statistical analysis description:

Progression Free Survival (PFS) in Participants With an Elevated Screening Lactate Dehydrogenase (eLDH)

Comparison groups	Ganetespib and Docetaxel v Docetaxel

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5191 [23]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.797
upper limit	1.551

Notes:

[23] - Significance level of 0.05. P-value was from stratified log-rank test (strata: screening ECOG and geographic region).

Secondary: Objective Response Rate (ORR) in Participants With an Elevated Screening Lactate Dehydrogenase (eLDH) as of 19 October 2015

End point title	Objective Response Rate (ORR) in Participants With an Elevated Screening Lactate Dehydrogenase (eLDH) as of 19 October 2015

End point description:

Percentage of participants whose best overall response, as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST 1.1), was either a complete response (CR) or a partial response (PR).
CR was defined as the disappearance (or normalization) of all target lesions.
PR was defined as at least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
Elevated LDH includes values above the upper limit of normal.
Data were not summarized due to the early termination of the study due to futility.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[24]	0[25]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[24] - Data were not summarized due to the early termination of the study due to futility.

[25] - Data were not summarized due to the early termination of the study due to futility.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) in Participants With an Elevated Screening Lactate Dehydrogenase (eLDH) as of 19 October 2015

End point title	Disease Control Rate (DCR) in Participants With an Elevated Screening Lactate Dehydrogenase (eLDH) as of 19 October

	2015

End point description:

Percentage of participants whose best overall response, as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST 1.1), was a complete response (CR), a partial response (PR), or stable disease (SD).
CR was defined as the disappearance (or normalization) of all target lesions.
PR was defined as <=30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of diameters while on study. The duration of SD must be for at least 6 weeks or 12 weeks.
Elevated LDH includes values above the upper limit of normal.
Data were not summarized due to the early termination of the study due to futility.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[26]	0[27]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[26] - Data were not summarized due to the early termination of the study due to futility.

[27] - Data were not summarized due to the early termination of the study due to futility.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate for Time to Emergence of New Metastatic Lesion (TNL) as of 19 October 2015

End point title	Kaplan-Meier Estimate for Time to Emergence of New Metastatic Lesion (TNL) as of 19 October 2015

End point description:

TNL was defined as time from the randomization date to the first day of radiological progression that included new metastatic lesions. Participants with no new metastatic lesions were censored at the date of the most recent radiological assessment.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335[28]	337[29]		
Units: months				
median (confidence interval 95%)	8.1 (6.5 to 9.7)	8.7 (7.2 to 11.6)		

Notes:

[28] - Randomized patients

[29] - Randomized patients

Statistical analyses

Statistical analysis title	Time to New Metastatic Lesion
Comparison groups	Docetaxel v Ganetespib and Docetaxel
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1343 [30]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.233
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.937
upper limit	1.621

Notes:

[30] - Significance level of 0.05. Stratified log-rank test (strata: screening LDH, screening ECOG and geographic region).

Secondary: Percentage of Participants With Progressive Disease Due to Any New Metastatic Lesion as of 19 October 2015

End point title	Percentage of Participants With Progressive Disease Due to Any New Metastatic Lesion as of 19 October 2015

End point description:

Progressive disease was due to either new metastatic lesions only or new metastatic lesions and target tumor growth.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335[31]	337[32]		
Units: percentage of participants				
number (not applicable)	34.9	30.6		

Notes:

[31] - Randomized participants

[32] - Randomized participants

Statistical analyses

Statistical analysis title	PD Due to New Metastatic Lesion
Comparison groups	Ganetespib and Docetaxel v Docetaxel
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [33]
Method	Fisher exact

Notes:

[33] - Significance level of 0.05.

Secondary: Participants With Treatment-Emergent Adverse Events as of 23 December 2015

End point title	Participants With Treatment-Emergent Adverse Events as of 23 December 2015

End point description:

Treatment-emergent adverse events (AEs) were defined as AEs that occurred from the time of first dose through 30 days after the last dose of study medication. The Investigator graded the severity of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria:
Grade 1 = Mild Grade 2 = Moderate Grade 3 = Severe Grade 4 = Life threatening Grade 5 = Death A Serious AE (SAE) is defined as any AE which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or constitutes an important medical event.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338[34]	342[35]		
Units: participants				
>=1 AE	317	307		
>=1 AE with CTCAE grade of 3 or 4	222	184		
>=1 SAE	139	107		
>=1 AE leading to dose reduction	61	37		
>=1 AE leading to delayed dose	125	55		
>=1 AE leading to study drug discontinuation	31	36		
>=1 SAE leading to study drug discontinuation	19	15		
>=1 SAE leading to hospitalization	109	87		
>=1 SAE with outcome of death	40	30		
>=1 AE with first occurrence during Cycle 1-2	280	280		
>=1 AE with first occurrence during Cycle 1-4	304	299		
>=1 AE with first occurrence during Cycle 1-6	312	302		

Notes:

[34] - Safety population

[35] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-Reported Quality of Life as Measured by the European Quality Of Life - Five Dimensions - Three Levels (EQ-5D-3L) Survey

End point title	Patient-Reported Quality of Life as Measured by the European Quality Of Life - Five Dimensions - Three Levels (EQ-5D-3L) Survey

End point description:

The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. An overall EQ-5D-3L index was calculated (see EuroQoL website, http://www.euroqol.org/eq-5d-products/eq-5d-3l.html), with an index of 1.0 representing full health and and "0" represents dead, with some health states being worse than dead (<"0").
Data were not summarized due to the early termination of the study due to futility.

End point type	Secondary

End point timeframe:

Day 1 (pre-treatment), Day 63 (Cycle 3 Day 1), Day 105 (Cycle 5 Day 1) and end of trial

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[36]	0[37]		
Units: participants				

Notes:

[36] - Data were not summarized due to the early termination of the study due to futility.

[37] - Data were not summarized due to the early termination of the study due to futility.

Statistical analyses

No statistical analyses for this end point

Secondary: Patient-Reported Symptom Improvement as Measured by the Functional Assessment of Cancer Therapy - Lung (FACT-L) Version 4 Test

End point title	Patient-Reported Symptom Improvement as Measured by the Functional Assessment of Cancer Therapy - Lung (FACT-L) Version 4 Test

End point description:

The FACT-L contains 4 general subscales and a Lung Cancer Subscale (LCS). General subscales include: Physical Well-Being (PWB), Social/ Family Well-Being (SWB), Emotional Well-Being (EWB), and Functional Well-Being (FWB). The LCS assesses symptoms commonly reported by lung cancer patients (e.g., shortness of breath, weight loss, and tightness in the chest). The FACT-L total score ranges from 0 to 136, higher scores represent better QOL.
Data were not summarized due to the early termination of the study due to futility.

End point type	Secondary

End point timeframe:

Day 1 (pre-treatment), Day 63 (Cycle 3 Day 1), Day 105 (Cycle 5 Day 1) and end of trial

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[38]	0[39]		
Units: participants				

Notes:

[38] - Data were not summarized due to the early termination of the study due to futility.

[39] - Data were not summarized due to the early termination of the study due to futility.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Exploratory Biomarker Analyses

End point title	Exploratory Biomarker Analyses

End point description:

Exploratory biomarker analyses was to assess correlation between biomarkers and clinical outcome. However data were not analyzed due to the early termination of the study due to futility.

End point type	Other pre-specified

End point timeframe:

up to 36 months

End point values	Ganetespib and Docetaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[40]	0[41]		
Units: participants				

Notes:

[40] - Data were not analyzed due to the early termination of the study due to futility.

[41] - Data were not analyzed due to the early termination of the study due to futility.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 36 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Docetaxel
Reporting group description: Docetaxel (75 mg/m^2) was administered on Day 1 of a 3-week treatment cycle by 1-hour IV infusion.	
Reporting group title	Ganetespib and Docetaxel
Reporting group description: Ganetespib (150 mg/m^2) and docetaxel (75 mg/m^2) were administered as separate 1-hour IV infusions on Day 1 of each 3-week treatment cycle. Administration of ganetespib preceded the administration of docetaxel. Ganetespib was administered again on Day 15 of each cycle.	

Serious adverse events	Docetaxel	Ganetespib and Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	107 / 342 (31.29%)	139 / 338 (41.12%)	
number of deaths (all causes)	175	195	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	11 / 342 (3.22%)	16 / 338 (4.73%)	
occurrences causally related to treatment / all	0 / 11	1 / 16	
deaths causally related to treatment / all	0 / 10	0 / 11	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	0 / 342 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertension			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 342 (0.58%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 342 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 342 (0.58%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cancer surgery			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 342 (0.29%)	7 / 338 (2.07%)	
occurrences causally related to treatment / all	1 / 1	7 / 9	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chest pain			
subjects affected / exposed	3 / 342 (0.88%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 342 (1.17%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Fatigue			
subjects affected / exposed	2 / 342 (0.58%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 342 (0.58%)	5 / 338 (1.48%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Multi-organ failure			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 342 (0.00%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated hernia			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden cardiac death			
subjects affected / exposed	3 / 342 (0.88%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Sudden death			
subjects affected / exposed	0 / 342 (0.00%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 3	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunodeficiency			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory failure			
subjects affected / exposed	1 / 342 (0.29%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 2	
Aspiration			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	11 / 342 (3.22%)	9 / 338 (2.66%)	
occurrences causally related to treatment / all	1 / 12	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 2	
Haemoptysis			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 342 (1.17%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 342 (0.29%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 342 (0.29%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	5 / 342 (1.46%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pulmonary fibrosis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 342 (0.29%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 342 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 342 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infusion related reaction			
subjects affected / exposed	2 / 342 (0.58%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 342 (0.29%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			

subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 342 (0.29%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersomnia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Loss of consciousness			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 342 (0.29%)	4 / 338 (1.18%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 342 (0.88%)	6 / 338 (1.78%)	
occurrences causally related to treatment / all	3 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	11 / 342 (3.22%)	19 / 338 (5.62%)	
occurrences causally related to treatment / all	10 / 11	20 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 342 (0.29%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	10 / 342 (2.92%)	12 / 338 (3.55%)	
occurrences causally related to treatment / all	14 / 15	13 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Constipation			
subjects affected / exposed	2 / 342 (0.58%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	2 / 342 (0.58%)	15 / 338 (4.44%)	
occurrences causally related to treatment / all	1 / 2	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry mouth			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Large intestinal obstruction			

subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nausea			
subjects affected / exposed	1 / 342 (0.29%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stomatitis			
subjects affected / exposed	1 / 342 (0.29%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 342 (0.58%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis toxic			

subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 342 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (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			
Arthralgia			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 342 (0.29%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			

subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (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			
Anal abscess			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 342 (1.17%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 342 (0.29%)	5 / 338 (1.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 342 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 342 (0.29%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 342 (0.29%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 342 (0.29%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 342 (0.29%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 342 (0.58%)	12 / 338 (3.55%)	
occurrences causally related to treatment / all	1 / 2	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pseudomembranous colitis			

subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 342 (0.58%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	1 / 342 (0.29%)	4 / 338 (1.18%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 342 (0.29%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 342 (0.88%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 342 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Docetaxel	Ganetespib and Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	293 / 342 (85.67%)	308 / 338 (91.12%)	
Investigations			
Weight decreased			
subjects affected / exposed	18 / 342 (5.26%)	38 / 338 (11.24%)	
occurrences (all)	22	50	

Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	11 / 342 (3.22%)	17 / 338 (5.03%)	
occurrences (all)	13	32	
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 342 (6.14%)	24 / 338 (7.10%)	
occurrences (all)	30	41	
Headache			
subjects affected / exposed	17 / 342 (4.97%)	22 / 338 (6.51%)	
occurrences (all)	23	30	
Neuropathy peripheral			
subjects affected / exposed	33 / 342 (9.65%)	41 / 338 (12.13%)	
occurrences (all)	52	63	
Peripheral sensory neuropathy			
subjects affected / exposed	23 / 342 (6.73%)	15 / 338 (4.44%)	
occurrences (all)	29	18	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	70 / 342 (20.47%)	59 / 338 (17.46%)	
occurrences (all)	144	106	
Leukopenia			
subjects affected / exposed	18 / 342 (5.26%)	20 / 338 (5.92%)	
occurrences (all)	54	39	
Neutropenia			
subjects affected / exposed	94 / 342 (27.49%)	109 / 338 (32.25%)	
occurrences (all)	255	243	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	48 / 342 (14.04%)	51 / 338 (15.09%)	
occurrences (all)	109	100	
Chest pain			
subjects affected / exposed	17 / 342 (4.97%)	19 / 338 (5.62%)	
occurrences (all)	20	26	
Fatigue			

subjects affected / exposed	72 / 342 (21.05%)	79 / 338 (23.37%)	
occurrences (all)	123	130	
Oedema peripheral			
subjects affected / exposed	29 / 342 (8.48%)	28 / 338 (8.28%)	
occurrences (all)	30	39	
Pyrexia			
subjects affected / exposed	19 / 342 (5.56%)	26 / 338 (7.69%)	
occurrences (all)	30	33	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	26 / 342 (7.60%)	35 / 338 (10.36%)	
occurrences (all)	31	41	
Diarrhoea			
subjects affected / exposed	47 / 342 (13.74%)	149 / 338 (44.08%)	
occurrences (all)	64	327	
Nausea			
subjects affected / exposed	68 / 342 (19.88%)	59 / 338 (17.46%)	
occurrences (all)	103	86	
Stomatitis			
subjects affected / exposed	36 / 342 (10.53%)	32 / 338 (9.47%)	
occurrences (all)	52	40	
Vomiting			
subjects affected / exposed	23 / 342 (6.73%)	36 / 338 (10.65%)	
occurrences (all)	27	46	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 342 (9.06%)	34 / 338 (10.06%)	
occurrences (all)	36	45	
Dyspnoea			
subjects affected / exposed	41 / 342 (11.99%)	55 / 338 (16.27%)	
occurrences (all)	56	59	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	84 / 342 (24.56%)	76 / 338 (22.49%)	
occurrences (all)	98	93	
Rash			

subjects affected / exposed	16 / 342 (4.68%)	19 / 338 (5.62%)	
occurrences (all)	20	21	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 342 (2.34%)	23 / 338 (6.80%)	
occurrences (all)	8	23	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 342 (5.85%)	17 / 338 (5.03%)	
occurrences (all)	35	24	
Back pain			
subjects affected / exposed	14 / 342 (4.09%)	24 / 338 (7.10%)	
occurrences (all)	19	28	
Bone pain			
subjects affected / exposed	17 / 342 (4.97%)	19 / 338 (5.62%)	
occurrences (all)	24	26	
Myalgia			
subjects affected / exposed	28 / 342 (8.19%)	38 / 338 (11.24%)	
occurrences (all)	52	64	
Pain in extremity			
subjects affected / exposed	15 / 342 (4.39%)	18 / 338 (5.33%)	
occurrences (all)	19	23	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	35 / 342 (10.23%)	52 / 338 (15.38%)	
occurrences (all)	49	66	
Hyponatraemia			
subjects affected / exposed	9 / 342 (2.63%)	26 / 338 (7.69%)	
occurrences (all)	20	46	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2013	New secondary objective added: "Evaluate and compare the emergence of metastatic lesions in the two treatment groups".
10 March 2014	The patient population was revised to a "Target Patient Population" (TPP) defined as: Patients with second-line advanced NSCLC of adenocarcinoma histology diagnosed ≥6 months prior to study entry whose tumors are negative for both EGFR mutations and ALK translocations. Secondary endpoints were added: Compare PFS between the 2 treatment arms in TPP and Compare OS between the 2 treatment arms in patients with eLDH at screening in TPP. Removed duration of treatment (DOT) as a secondary endpoint. Removed mutant KRAS as a population in which to compare OS, PFS, ORR, and DCR. KRAS status was included within the objective of "Assess the correlation between biomarkers, including KRAS status, and clinical outcome." Increased sample size from N=500 to N=850 Increased number of study centers from up to 140 to up to 250 Increased duration of recruitment to 28 months including a prolonged ramp-up period.
17 November 2014	The primary analysis population was revised to all randomized patients. Secondary efficacy endpoints and analyses were revised from PFS in the TPP and OS for eLDH patients in the TPP to PFS for all randomized patients and OS for patients with eLDH. Other Secondary Efficacy Endpoints and Analyses were revised to a single subpopulation of interest, patients with eLDH at screening, for whom PFS will be analyzed. The "Other Secondary Objective" to compare OS in patients with eLDH5 was removed.
17 August 2015	The number of patients for combination arm (N=425) was added. Addition of a +/- 15 minute window to the rest period between ganetespib and docetaxel infusion. Addition of "Dose may also be recalculated for a weight change of <10%". Other administrative changes. No changes in primary or secondary endpoints.
21 September 2015	Addition of gastrointestinal perforation as an identified risk with ganetespib.

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.

The study was stopped after the first Interim Analysis due to futility. Efficacy is based on a 05-10-2015 data cut for the first interim analysis. Safety is based on the final database locked on 23-12-2015.

Notes: