



Clinical trial results:

A Randomized, Double-blind, Placebo-Controlled, Phase 2 Clinical Trial of Alisertib (MLN8237) in Combination With Paclitaxel Versus Placebo in Combination With Paclitaxel as Second Line Therapy for Small Cell Lung Cancer (SCLC)

Summary

EudraCT number	2013-003713-18
Trial protocol	BE HU CZ ES DE IT PL
Global end of trial date	10 July 2017

Results information

Result version number	v1 (current)
This version publication date	11 March 2018
First version publication date	11 March 2018

Trial information

Trial identification

Sponsor protocol code	C14018
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02038647
WHO universal trial number (UTN)	U1111-1154-9805

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA, United States, 02139
Public contact	Medical Director, Takeda, +1877 8253327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Takeda, +1877 8253327, trialdisclosures@takeda.com

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	10 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2016
Global end of trial reached?	Yes
Global end of trial date	10 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to determine if the combination treatment can improve progression free survival (defined as the time from the date of randomization to the date of first documentation of disease progression or death, whichever occurs first) when compared with placebo + paclitaxel.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 70
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 17
Worldwide total number of subjects	178
EEA total number of subjects	96

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	107
From 65 to 84 years	70
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 54 investigative sites in the United States, Canada, European Union (Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland and Spain) from 12 May 2014 to 10 July 2017. Data cutoff for the primary analysis was 3 January 2016.

Pre-assignment

Screening details:

Participants with a diagnosis of Small Cell Lung Cancer (SCLC) were enrolled in 1 of 2 treatment groups: alisertib + paclitaxel or placebo + paclitaxel arm group.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Alisertib + Paclitaxel

Arm description:

Alisertib 40 mg, tablets, orally, twice a day, 3 days on/4 days off for 3 weeks on Days 1-3, 8-10, and 15-17 in a 28-day cycle along with paclitaxel 60 mg/m² intravenously (IV) once a week for 3 weeks on Days 1, 8, and 15 in a 28-day cycle until disease progression (Up to 17 Cycles).

Arm type	Experimental
Investigational medicinal product name	Alisertib
Investigational medicinal product code	MLN8237
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alisertib Tablets

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel IV

Arm title	Placebo + Paclitaxel
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Arm description:

Alisertib placebo-matching tablets, orally, twice a day, 3 days on/4 days off for 3 weeks on Days 1-3, 8-10, and 15-17 in a 28-day cycle along with paclitaxel 80 mg/m² IV once a week for 3 weeks on Days 1, 8, and 15 in a 28-day cycle until disease progression (Up to 22 Cycles).

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

Number of subjects in period 1	Alisertib + Paclitaxel	Placebo + Paclitaxel
Started	89	89
Completed	0	0
Not completed	89	89
Consent withdrawn by subject	5	2
Not Reported	-	1
Adverse event, non-fatal	18	10
Ongoing at Datacut	9	10
Progressive Disease	50	59
Symptomatic Deterioration	7	7

Baseline characteristics

Reporting groups

Reporting group title	Alisertib + Paclitaxel
Reporting group description:	
Alisertib 40 mg, tablets, orally, twice a day, 3 days on/4 days off for 3 weeks on Days 1-3, 8-10, and 15-17 in a 28-day cycle along with paclitaxel 60 mg/m ² intravenously (IV) once a week for 3 weeks on Days 1, 8, and 15 in a 28-day cycle until disease progression (Up to 17 Cycles).	
Reporting group title	Placebo + Paclitaxel
Reporting group description:	
Alisertib placebo-matching tablets, orally, twice a day, 3 days on/4 days off for 3 weeks on Days 1-3, 8-10, and 15-17 in a 28-day cycle along with paclitaxel 80 mg/m ² IV once a week for 3 weeks on Days 1, 8, and 15 in a 28-day cycle until disease progression (Up to 22 Cycles).	

Reporting group values	Alisertib + Paclitaxel	Placebo + Paclitaxel	Total
Number of subjects	89	89	178
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	61.8	63.4	
standard deviation	± 8.55	± 8.56	-
Gender, Male/Female			
Units: Subjects			
Female	38	39	77
Male	51	50	101
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic or Latino	81	84	165
Unknown or Not Reported	6	1	7
Missing	0	1	1
Race/Ethnicity, Customized			
Units: Subjects			
White	83	83	166
Black or African American	3	2	5
Not reported	2	2	4
Asian	1	0	1
Other	0	1	1
Missing	0	1	1
Region of Enrollment			
Units: Subjects			
Belgium	8	8	16
Czech Republic	6	5	11
France	7	5	12
Germany	2	1	3
Hungary	16	15	31
Italy	2	0	2
Poland	1	3	4

Spain	6	11	17
Canada	6	6	12
United States	35	35	70
Height			
Data is available only for 86 and 87 participants respectively.			
Units: cm			
arithmetic mean	169.5	168.8	
standard deviation	± 10.43	± 9.52	-
Weight			
Units: kg			
arithmetic mean	78.47	75.26	
standard deviation	± 20.561	± 17.602	-
Body Surface Area			
Body surface area=square root of (height [cm]*weight [kg]/3600). Data is available only for 86 and 87 participants respectively.			
Units: m ²			
arithmetic mean	1.911	1.872	
standard deviation	± 0.2829	± 0.2433	-

End points

End points reporting groups

Reporting group title	Alisertib + Paclitaxel
Reporting group description: Alisertib 40 mg, tablets, orally, twice a day, 3 days on/4 days off for 3 weeks on Days 1-3, 8-10, and 15-17 in a 28-day cycle along with paclitaxel 60 mg/m ² intravenously (IV) once a week for 3 weeks on Days 1, 8, and 15 in a 28-day cycle until disease progression (Up to 17 Cycles).	
Reporting group title	Placebo + Paclitaxel
Reporting group description: Alisertib placebo-matching tablets, orally, twice a day, 3 days on/4 days off for 3 weeks on Days 1-3, 8-10, and 15-17 in a 28-day cycle along with paclitaxel 80 mg/m ² IV once a week for 3 weeks on Days 1, 8, and 15 in a 28-day cycle until disease progression (Up to 22 Cycles).	

Primary: Progression-Free Survival (PFS) as determined by Investigator, analyzed using FDA Guidelines

End point title	Progression-Free Survival (PFS) as determined by Investigator, analyzed using FDA Guidelines
End point description: PFS is defined as time in days from start of study treatment to first documentation of objective tumor progression based on Investigator's assessment or up to death due to any cause, whichever occurs first based on Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1. Progressive disease (PD) was defined as $\geq 20\%$ increase in sum longest diameter (LD) in reference to the smallest on-study sum LD, or the appearance of new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.	
End point type	Primary
End point timeframe: Every cycle for first 6 months and then every 2 months until disease progression or death or up to data cut-off: 03 January 2016 (approximately 22 months)	

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	89		
Units: days				
median (confidence interval 95%)	101 (80 to 113)	66 (53 to 83)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alisertib + Paclitaxel v Placebo + Paclitaxel

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.113 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.557
upper limit	1.067

Notes:

[1] - P-value tests the hypothesis of equal event times in both treatment arms obtained using the Log-rank test stratified by disease subtype as sensitive versus resistant/refractory and the presence of brain metastases.

Secondary: Percentage of Participants who Experience at least one Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants who Experience at least one Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)
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End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with treatment. An AE can be any unfavorable and unintended sign (eg, clinically significant abnormal laboratory finding), symptom, or disease temporally associated with use of drug, whether or not it is considered related to drug. A treatment-emergent adverse event (TEAE) is defined as an AE with an onset that occurs after receiving study drug. A Serious Adverse Event (SAE) is any experience that suggests significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is congenital anomaly/birth defect or is medically significant per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

End point type	Secondary
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End point timeframe:

From the first dose through 30 days after the last dose of study medication: data cut-off 03 January 2016 (Up to 10.8 months)

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	89		
Units: percentage of participants				
TEAEs	99	96		
SAEs	44	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS was defined as the time in days from the date of randomization to the date of death due to any cause.	
End point type	Secondary
End point timeframe:	
Contact every 2 months after EOT/disease progression until the sooner of death, study closure, or 14 months after the last participant was randomized up to data cut-off: 3 January 2016 (approximately 22 months)	

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	89		
Units: days				
median (confidence interval 95%)	186 (150 to 219)	165 (128 to 183)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alisertib + Paclitaxel v Placebo + Paclitaxel
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.714 ^[2]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.652
upper limit	1.341

Notes:

[2] - P-value tests the hypothesis of equal event times in both treatment arms obtained using the Log-rank test stratified by disease subtype as sensitive versus resistant/refractory and the presence of brain metastases.

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
End point description:	
ORR is defined as the percentage of participants who achieved CR or partial response (PR) as best response based on Investigator's assessment according to RECIST v 1.1. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumor marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR was defined as ≥ 30% decrease in sum of LD of target lesions in reference to Baseline sum LD.	
End point type	Secondary

End point timeframe:

Baseline until disease progression, death or EOT up to data cut-off: 03 January 2016 (approximately 9.8 months)

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	89		
Units: percentage of participants				
number (confidence interval 95%)	22 (14 to 33)	18 (11 to 28)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alisertib + Paclitaxel v Placebo + Paclitaxel
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.406 ^[3]
Method	Weighted Cochran-Mantel-Haenszel test
Parameter estimate	Odds ratio (OR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.55

Notes:

[3] - Stratification factors were disease subtypes (sensitive versus resistant/refractory), the presence of brain metastases and region.

Secondary: Complete Response Rate (CRR)

End point title	Complete Response Rate (CRR)
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End point description:

CRR is defined as the percentage of participants who achieved CR as best response and based on Investigator's assessment according to RECIST v 1.1. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumor marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

End point type	Secondary
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End point timeframe:

Baseline until disease progression, death or EOT up to data cut-off: 03 January 2016 (approximately 9.8 months)

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	89		
Units: percentage of participants				
number (confidence interval 95%)	1 (1 to 6)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alisertib + Paclitaxel v Placebo + Paclitaxel
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.283 ^[4]
Method	Weighted Cochran-Mantel-Haenszel test
Parameter estimate	Odds ratio (OR)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	9999.99

Notes:

[4] - Stratification factors were disease subtypes (sensitive versus resistant/refractory), the presence of brain metastases and region.

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
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End point description:

DCR was defined as the percentage of participants who achieved CR, PR, or SD (when SD was a minimum of 8 weeks in duration). Duration of SD was defined as the time from the date of randomization to the date of first documentation of disease progression for participants who achieved SD as their best overall response. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumor marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR was defined as $\geq 30\%$ decrease in sum of LD of target lesions in reference to Baseline sum LD. PD was defined as $\geq 20\%$ increase in sum LD in reference to the smallest on-study sum LD, or the appearance of new lesions. 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
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End point timeframe:

Baseline until disease progression, death or EOT up to data cut-off: 03 January 2016 (approximately 9.8 months)

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	89		
Units: percentage of participants				
number (confidence interval 95%)	58 (47 to 69)	46 (35 to 57)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alisertib + Paclitaxel v Placebo + Paclitaxel
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.077 ^[5]
Method	Weighted Cochran-Mantel-Haenszel test
Parameter estimate	Odds ratio (OR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.08

Notes:

[5] - Stratification factors were disease subtypes (sensitive versus resistant/refractory), the presence of brain metastases and region.

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)
End point description:	DOR was defined as the time from the date of first documentation of a PR or better to the date of first documentation of PD for responders. PR was defined as $\geq 30\%$ decrease in sum of longest diameter (LD) of target lesions in reference to Baseline sum LD. PD was defined as $\geq 20\%$ increase in sum LD in reference to the smallest on-study sum LD, or the appearance of new lesions. 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:	From first documented response until disease progression until data cut-off 03 January 2016 (approximately 9.8 months)

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	16		
Units: days				
median (confidence interval 95%)	96 (84 to 141)	85 (58 to 177)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Symptom (QLQ-LC13 Cough Scale, QLQ-C30 Dyspnea Scale, QLQ-C30 Pain Scale) Score at Cycle 5

End point title	Change from Baseline in Symptom (QLQ-LC13 Cough Scale, QLQ-C30 Dyspnea Scale, QLQ-C30 Pain Scale) Score at Cycle 5
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End point description:

European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 is 30-item questionnaire with 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (fatigue, nausea, vomiting and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Most questions use 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions use 7-point scale (1=very poor – 7=Excellent). Total Score=0-100 scale; for 5 functional scales and global quality-of-life scale, a higher score=a better level of functioning. For symptoms scale, higher score= higher level of symptoms. EORTC QLQ-LC13 is considered as standard instrument to assess the quality of life (QL) of lung cancer participants. Total Score=0-100. Higher score=increase in level of symptomatology. The change between (QLQ-LC13 Cough Scale, QLQ-C30 Dyspnea Scale, QLQ-C30 Pain Scale) score collected at Cycle 5 relative to baseline.

End point type	Secondary
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End point timeframe:

Baseline up to Cycle 5 (approximately 4.6 months)

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	15		
Units: score on a scale				
least squares mean (standard error)				
Change at Cycle 5, QLQ-LC-13 Cough Scale	-10.94 (± 3.07)	8.07 (± 6.04)		
Change at Cycle 5, QLQ-C30 Dyspnea Scale	-3.48 (± 4.25)	-1.09 (± 2.92)		
Change at Cycle 5, QLQ-C30 Pain Scale	-4.82 (± 4.86)	-4.88 (± 5.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Symptom Relief

End point title	Percentage of Participants Experiencing Symptom Relief
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End point description:

Percentage of participants experiencing symptom relief, including coughing relief, dyspnea relief, and pain relief. Coughing relief is defined as a decrease from baseline ≥ 10 in QLQ-LC13 cough scale/item

score. Dyspnea relief is defined as a decrease from baseline ≥ 10 in QLQ-C30 dyspnea scale/item score. Pain relief is defined as a decrease from baseline ≥ 10 in QLQ-C30 pain scale score. EORTC QLQ-C30 is 30-item questionnaire with 5 functional scales, 1 global health status scale, 3 symptom scales, 6 single items. Total Score=0-100 scale; for 5 functional scales and global quality-of-life scale, a higher score=a better level of functioning. For symptoms scale, higher score= higher level of symptoms. EORTC QLQ-LC13 is considered as standard instrument to assess the QL of lung cancer participants. Total Score=0-100. Higher score=increase in level of symptomatology.

End point type	Secondary
End point timeframe:	
Baseline up to Cycle 11, data cut-off: 03 January 2016 (approximately 9.8 months)	

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	89		
Units: percentage of participants				
number (confidence interval 95%)				
Coughing Relief	28 (19 to 39)	24 (15 to 34)		
Dyspnea Relief	31 (22 to 42)	16 (9 to 25)		
Pain Relief	39 (29 to 50)	36 (26 to 47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom Relief

End point title	Time to Symptom Relief
End point description:	
Time to symptom (coughing/dyspnea/pain) relief was defined as the time from the date of randomization to the date of first detection of coughing/dyspnea/pain relief, respectively. Here, 9999=Not Estimable as median was not reached due to low number of participants with events and 99999= Not Estimable as upper limit of CI was not reached due to low number of participants with events.	
End point type	Secondary
End point timeframe:	
Baseline up to Cycle 11, data cut-off: 03 January 2016 (approximately 9.8 months)	

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	89		
Units: months				
median (confidence interval 95%)				
Time to Coughing Relief	9999 (7.6 to 9999)	9999 (9999 to 9999)		
Time to Dyspnea Relief	99999 (99999 to 99999)	99999 (99999 to 99999)		

Time to Pain Relief	3.0 (1.9 to 99999)	3.7 (1.1 to 99999)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom Progression

End point title	Time to Symptom Progression
End point description:	
Time to coughing/dyspnea/pain progression (prg) was time from the date of randomization to first detection of prg.Coughing prg was rise from baseline \geq 10 in QLQ-LC13 cough scale (scl) score.Dyspnea prg was rise from baseline \geq 10 in QLQ-C30 dyspnea scl score.Pain prg was rise from baseline \geq 10 in QLQ-C30 pain scl score.EORTC QLQ-C30 is 30-item questionnaire with 5 functional scls (physical,role,emotional,cognitive,social),1global health status scl,3symptom (symp)scls(fatigue,nausea,vomiting,pain),6single items(dyspnea,insomnia,appetite loss,constipation,diarrhea,financial difficulties).The QLQ-LC13 is 13-item scl for rate treatment-specific symps in lung cancer.Total Score= 0-100 scl; for 5 functional and global quality-of-life scl,higher score=better level of functioning and same for symps scl.Here, 9999=Not Estimable (NE) as median was not reached due to low number of participants with events,99999= NE as upper limit of CI was not	
End point type	Secondary
End point timeframe:	
Baseline up to Cycle 11, data cut-off: 03 January 2016 (approximately 9.8 months)	

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	89		
Units: months				
median (confidence interval 95%)				
Time to Coughing Progression	9999 (9999 to 9999)	2.8 (2.2 to 6.3)		
Time to Dyspnea Progression	3.7 (1.9 to 99999)	4.6 (1.9 to 6.3)		
Time to Pain Progression	2.9 (2.1 to 99999)	2.8 (1.9 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Plasma Concentration for Alisertib and Paclitaxel

End point title	Observed Plasma Concentration for Alisertib and Paclitaxel
End point description:	
End point type	Secondary

End point timeframe:

Day 1 pre-dose and at multiple timepoints (up to 11 hours) post-dose; Day 8, 2 hours post-dose; Day 15, 1 hour pre-dose

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[6]	0 ^[7]		
Units: nM				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - Less PK sampling planned for alisertib PK,exposure-response analysis not done due to program status

[7] - Less PK sampling planned for alisertib PK,exposure-response analysis not done due to program status

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Quality of Life (HRQOL)

End point title	Health Related Quality of Life (HRQOL)
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End point description:

End point type	Secondary
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End point timeframe:

Baseline up to Cycle 11, data cut-off: 03 January 2016 (approximately 9.8 months)

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[8]	0 ^[9]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - Due to change in planned analysis, data was not analyzed for this outcome measure.

[9] - Due to change in planned analysis, data was not analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarker Correlative Studies including Circulating Tumor Cells and Circulating DNA Assessments

End point title	Biomarker Correlative Studies including Circulating Tumor Cells and Circulating DNA Assessments
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 cycle 1 in a 28-day cycle

End point values	Alisertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[10]	0 ^[11]		
Units: percentage of participants				
number (not applicable)				

Notes:

[10] - Due to change in planned analysis, data was not analyzed for this outcome measure.

[11] - Due to change in planned analysis, data was not analyzed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug through 30 days after the last dose of study drug (Up to 646 Days)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Placebo + Paclitaxel
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Reporting group description:

Alisertib placebo-matching tablets, orally, twice a day, 3 days on/4 days off for 3 weeks on Days 1-3, 8-10, and 15-17 in a 28-day cycle along with paclitaxel 80 mg/m² IV once a week for 3 weeks on Days 1, 8, and 15 in a 28-day cycle until disease progression (Up to 22 Cycles).

Reporting group title	Alisertib + Paclitaxel
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Reporting group description:

Alisertib 40 mg, tablets, orally, twice a day, 3 days on/4 days off for 3 weeks on Days 1-3, 8-10, and 15-17 in a 28-day cycle along with paclitaxel 60 mg/m² intravenously (IV) once a week for 3 weeks on Days 1, 8, and 15 in a 28-day cycle until disease progression (Up to 17 Cycles).

Serious adverse events	Placebo + Paclitaxel	Alisertib + Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 89 (33.71%)	39 / 87 (44.83%)	
number of deaths (all causes)	11	12	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer	Additional description: Four treatment-emergent deaths occurred during treatment in Placebo + Paclitaxel arm group and are not related with study drug.		
subjects affected / exposed	6 / 89 (6.74%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			

subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant	Additional description: Two treatment-emergent deaths occurred during treatment in Alisertib+ Paclitaxel arm group and are not related with study drug.		
subjects affected / exposed	0 / 89 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Glioblastoma			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic thrombosis	Additional description: One treatment-emergent death occurred during treatment in Alisertib + Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Embolism			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration	Additional description: One treatment-emergent death occurred during treatment in Placebo + Paclitaxel arm group and two treatment-emergent deaths occurred during treatment in Alisertib + Paclitaxel arm group and are not related with study drug.		

subjects affected / exposed	1 / 89 (1.12%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Fatigue			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
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			
Respiratory failure	Additional description: Two treatment-emergent death occurred during treatment in Alisertib+ Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	0 / 89 (0.00%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute respiratory failure	Additional description: One treatment-emergent death occurred during treatment in Placebo + Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	1 / 89 (1.12%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism	Additional description: One treatment-emergent death occurred during treatment in Placebo + Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	1 / 89 (1.12%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema	Additional description: One treatment-emergent death occurred during treatment in Alisertib + Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	1 / 89 (1.12%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 89 (2.25%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			

subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: One treatment-emergent death occurred during treatment in Alisertib + Paclitaxel arm group and is related with study drug.		
subjects affected / exposed	0 / 89 (0.00%)	9 / 87 (10.34%)	
occurrences causally related to treatment / all	0 / 0	9 / 12	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenia			
subjects affected / exposed	0 / 89 (0.00%)	5 / 87 (5.75%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia	Additional description: One treatment-emergent death occurred during treatment in Placebo + Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	1 / 89 (1.12%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 89 (0.00%)	5 / 87 (5.75%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stomatitis			
subjects affected / exposed	1 / 89 (1.12%)	4 / 87 (4.60%)	
occurrences causally related to treatment / all	1 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 89 (1.12%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 89 (2.25%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 89 (2.25%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis	Additional description: One treatment-emergent death occurred during treatment in Alisertib + Paclitaxel arm group and is related with study drug.		
subjects affected / exposed	0 / 89 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bacteraemia			

subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: One treatment-emergent death occurred during treatment in Alisertib + Paclitaxel arm group and is related with study drug.		
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock	Additional description: One treatment-emergent death occurred during treatment in Alisertib + Paclitaxel arm group and is related with study drug.		
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia	Additional description: One treatment-emergent death occurred during treatment in Placebo + Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	1 / 89 (1.12%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia	Additional description: One treatment-emergent death occurred during treatment in Placebo + Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 89 (1.12%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration	Additional description: One treatment-emergent death occurred during treatment in Placebo + Paclitaxel arm group and is not related with study drug.		
subjects affected / exposed	2 / 89 (2.25%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Paclitaxel	Alisertib + Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 89 (89.89%)	85 / 87 (97.70%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 89 (12.36%)	5 / 87 (5.75%)	
occurrences (all)	13	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 89 (31.46%)	38 / 87 (43.68%)	
occurrences (all)	35	52	
Asthenia			
subjects affected / exposed	11 / 89 (12.36%)	14 / 87 (16.09%)	
occurrences (all)	16	32	
Oedema peripheral			
subjects affected / exposed	10 / 89 (11.24%)	6 / 87 (6.90%)	
occurrences (all)	14	7	
Pyrexia			
subjects affected / exposed	6 / 89 (6.74%)	8 / 87 (9.20%)	
occurrences (all)	7	8	
Non-cardiac chest pain			
subjects affected / exposed	5 / 89 (5.62%)	4 / 87 (4.60%)	
occurrences (all)	5	5	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	19 / 89 (21.35%)	21 / 87 (24.14%)	
occurrences (all)	22	23	
Cough			
subjects affected / exposed	17 / 89 (19.10%)	17 / 87 (19.54%)	
occurrences (all)	18	19	
Productive cough			
subjects affected / exposed	9 / 89 (10.11%)	4 / 87 (4.60%)	
occurrences (all)	12	4	
Epistaxis			
subjects affected / exposed	7 / 89 (7.87%)	3 / 87 (3.45%)	
occurrences (all)	10	3	

Dysphonia subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3	5 / 87 (5.75%) 5	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 8	7 / 87 (8.05%) 7	
Confusional state subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 5	2 / 87 (2.30%) 2	
Investigations			
Neutrophil count decreased subjects affected / exposed occurrences (all)	4 / 89 (4.49%) 4	14 / 87 (16.09%) 28	
Weight decreased subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 7	13 / 87 (14.94%) 18	
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 4	12 / 87 (13.79%) 20	
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 4	5 / 87 (5.75%) 5	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	9 / 89 (10.11%) 14	15 / 87 (17.24%) 17	
Headache subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 7	9 / 87 (10.34%) 9	
Neuropathy peripheral subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 10	8 / 87 (9.20%) 10	
Paraesthesia			

subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 9	4 / 87 (4.60%) 5	
Hypoaesthesia subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 6	4 / 87 (4.60%) 5	
Somnolence subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3	5 / 87 (5.75%) 6	
Dysgeusia subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 5	2 / 87 (2.30%) 2	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	18 / 89 (20.22%) 23	38 / 87 (43.68%) 55	
Neutropenia subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 11	41 / 87 (47.13%) 89	
Leukopenia subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 8	12 / 87 (13.79%) 18	
Thrombocytopenia subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3	7 / 87 (8.05%) 7	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	18 / 89 (20.22%) 32	48 / 87 (55.17%) 104	
Nausea subjects affected / exposed occurrences (all)	30 / 89 (33.71%) 38	30 / 87 (34.48%) 43	
Vomiting subjects affected / exposed occurrences (all)	19 / 89 (21.35%) 27	28 / 87 (32.18%) 45	
Stomatitis			

subjects affected / exposed	6 / 89 (6.74%)	27 / 87 (31.03%)	
occurrences (all)	7	49	
Constipation			
subjects affected / exposed	21 / 89 (23.60%)	8 / 87 (9.20%)	
occurrences (all)	25	11	
Abdominal pain			
subjects affected / exposed	3 / 89 (3.37%)	12 / 87 (13.79%)	
occurrences (all)	4	13	
Abdominal pain upper			
subjects affected / exposed	6 / 89 (6.74%)	7 / 87 (8.05%)	
occurrences (all)	6	9	
Dyspepsia			
subjects affected / exposed	4 / 89 (4.49%)	8 / 87 (9.20%)	
occurrences (all)	4	9	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 89 (5.62%)	5 / 87 (5.75%)	
occurrences (all)	5	7	
Dysphagia			
subjects affected / exposed	3 / 89 (3.37%)	5 / 87 (5.75%)	
occurrences (all)	3	5	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 89 (5.62%)	14 / 87 (16.09%)	
occurrences (all)	5	15	
Rash maculo-papular			
subjects affected / exposed	6 / 89 (6.74%)	0 / 87 (0.00%)	
occurrences (all)	10	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 89 (5.62%)	9 / 87 (10.34%)	
occurrences (all)	10	12	
Muscular weakness			
subjects affected / exposed	6 / 89 (6.74%)	6 / 87 (6.90%)	
occurrences (all)	11	6	
Back pain			

subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 9	5 / 87 (5.75%) 8	
Musculoskeletal pain subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 5	4 / 87 (4.60%) 4	
Pain in extremity subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 7	3 / 87 (3.45%) 3	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 8	0 / 87 (0.00%) 0	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 5	2 / 87 (2.30%) 2	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	19 / 89 (21.35%) 26	29 / 87 (33.33%) 36	
Hypokalaemia subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 7	10 / 87 (11.49%) 12	
Dehydration subjects affected / exposed occurrences (all)	4 / 89 (4.49%) 5	7 / 87 (8.05%) 8	
Hypomagnesaemia subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 10	5 / 87 (5.75%) 5	
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1	7 / 87 (8.05%) 7	
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1	5 / 87 (5.75%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2014	The key purposes of Amendment 1 were to: • Modify and clarify the dose modification rules when managing hematologic or non-hematologic toxicities. • Remove the restrictions for 5-hydroxytryptamine 3 receptor antagonists. • Indicate that the dose could be reduced, if indicated, for participants who experienced sedation. • Increase the approximate number of study sites to be used in the study. • Add inclusion criterion 7 to allow participants requiring full systemic anticoagulation. • Modify inclusion criterion 12 regarding suitable venous access to remove reference to comparator arm. • Modify exclusion criterion 3 regarding prior treatment with an Aurora A specific-targeted or pan-Aurora-targeted agent. • Modify exclusion criterion 12 regarding diagnosis with another malignancy before the first dose of study drug. • Modify exclusion criterion 16 regarding infection to provide further definition. • Update language regarding the use of prophylactic antiemetic agents. • Update medical history to include disease stage and smoking history. • Update the extent of disease evaluation to include brain magnetic resonance imaging (MRI) with intravenous (IV) contrast (preferred) or computed tomography (CT) scan with IV contrast to be completed within 28 days before receiving the first dose of alisertib/placebo, irrespective of symptoms.
23 January 2015	The key purposes of Amendment 2 were to: •Clarify the definition of patient response to first-line chemotherapy. •Provide dose adjustment guidance for management of oral mucositis. •Add strong and moderate cytochrome P450 3A4 (CYP3A) inhibitors to list of excluded concomitant medications. •Remove collection of blood sample for profiling deoxyribonucleic acid (DNA) from circulating tumor cell (CTC), clarify that ctDNA samples would be used for biomarker assessment, and add blood sample collection for genomic DNA genetic characterization. •Remove "legal representative" as a potential party who may provide informed consent on behalf of participant. •Add text regarding requirement for treatment-specific pregnancy prevention guidelines for paclitaxel. •Update exclusion criterion restricting proton pump inhibitor (PPI) use to within 5 days prior to the first dose of study drug to maintain consistency in the restriction across alisertib clinical trials. •Update exclusion criteria regarding cardiovascular conditions and thromboembolic events. •Update exclusion criterion to exclude patients who had radiation therapy within the 2 weeks before study enrollment and had not fully recovered to stable clinical status. •Remove redundant information regarding the continuation of patients on study treatment following completion of the trial. •Remove the restriction of a maximum dose of diphenhydramine that was permitted for use as a premedication for paclitaxel-associated reactions. •Correct a typographical error in the dose modification rules regarding a repeat occurrence of hematologic toxicity after dosing for Arm A to indicate that alisertib dosing should remain the same for Days 1-3 and 8-10. •Indicate that patients were permitted to continue receiving study drug in cases where treatment assignment was inadvertently revealed. •Add collection of sparse paclitaxel pharmacokinetic (PK) samples to contribute to population PK analysis, and clarify timing of PK measurements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

