



Clinical trial results:

A randomized Phase III, double-blind, placebo-controlled multicenter trial of daily everolimus in combination with trastuzumab and vinorelbine, in pretreated women with HER2/neu over-expressing locally advanced or metastatic breast cancer

Summary

EudraCT number	2008-008697-31
Trial protocol	DE GR BE IT ES FR CZ GB HU SK
Global end of trial date	11 June 2015

Results information

Result version number	v1 (current)
This version publication date	27 June 2016
First version publication date	27 June 2016

Trial information

Trial identification

Sponsor protocol code	CRAD001W2301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01007942
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	11 June 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the combination of everolimus, vinorelbine and trastuzumab to the combination of vinorelbine and trastuzumab with respect to progression-free survival, based on local radiological review, in women with HER2/neu overexpressing advanced or metastatic breast cancer who are resistant to trastuzumab and have been pre-treated with a taxane.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2009
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	Argentina: 32
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	China: 49
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Japan: 57
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Spain: 32

Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	Turkey: 24
Country: Number of subjects enrolled	United States: 123
Worldwide total number of subjects	569
EEA total number of subjects	223

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)	472
From 65 to 84 years	97
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

DCO (Data cut-off) for patient disposition is 1-Apr-2015. Each Cycle = 21 days.

Patients completed = on treatment at time of DCO. Not Completed = ended treatment as per protocol.

Pre-assignment

Screening details:

284 patients were randomized to the Everolimus + trastuzumab +vinorelbine arm but only 280 took drug. 285 were randomized to the placebo + trastuzumab + vinorelbine arm but only 282 took drug.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus + vinorelbine + trastuzumab

Arm description:

Oral everolimus (5 mg/day) + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)

Arm type	Experimental
Investigational medicinal product name	everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral everolimus (5 mg/day) packaged in blister packs.

Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)

Investigational medicinal product name	vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

intravenous vinorelbine (25 mg/m2 weekly)

Arm title	placebo + vinorelbine + trastuzumab
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Arm description:

Oral daily matching placebo + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)

Arm type	Placebo
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Investigational medicinal product name	everolimus placebo
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral everolimus placebo (5 mg/day) packaged in blister packs.

Number of subjects in period 1	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab
Started	284	285
Completed	3	7
Not completed	281	278
Adverse event, serious fatal	3	2
Consent withdrawn by subject	19	14
Disease progression	217	242
Abnormal test procedure	-	1
Adverse event, non-fatal	29	14
New cancer therapy	5	1
Administrative problems	2	-
Patients Untreated	4	3
Lost to follow-up	1	-
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	Everolimus + vinorelbine + trastuzumab
Reporting group description:	
Oral everolimus (5 mg/day) + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)	
Reporting group title	placebo + vinorelbine + trastuzumab
Reporting group description:	
Oral daily matching placebo + intravenous vinorelbine (25 mg/m2 weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)	

Reporting group values	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab	Total
Number of subjects	284	285	569
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	230	242	472
From 65-84 years	54	43	97
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	54.3	53.4	
standard deviation	± 10.98	± 11	-
Gender, Male/Female Units: Participants			
Female	284	285	569
Male	0	0	0

End points

End points reporting groups

Reporting group title	Everolimus + vinorelbine + trastuzumab
Reporting group description: Oral everolimus (5 mg/day) + intravenous vinorelbine (25 mg/m ² weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)	
Reporting group title	placebo + vinorelbine + trastuzumab
Reporting group description: Oral daily matching placebo + intravenous vinorelbine (25 mg/m ² weekly) + intravenous trastuzumab (2 mg/kg weekly following a 4 mg/kg loading dose on Day 1 of Cycle 1 only)	
Subject analysis set title	Everolimus 2.5 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Oral everolimus of 2.5 mg/day	
Subject analysis set title	Everolimus 5mg/day
Subject analysis set type	Sub-group analysis
Subject analysis set description: Oral everolimus of 5 mg/day	
Subject analysis set title	Everolimus (Vinorelbine blood concentration)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Oral everolimus of 5 mg/day	
Subject analysis set title	Everolimus Placebo (Vinorelbine blood concentration)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Oral placebo everolimus of 5 mg/day	
Subject analysis set title	Everolimus (trastuzumab serum concentration)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Oral everolimus of 5 mg/day	
Subject analysis set title	Everolimus Placebo (trastuzumab serum concentration)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Oral placebo everolimus of 5 mg/day	

Primary: Progressive-free survival (PFS) per Investigator assessment

End point title	Progressive-free survival (PFS) per Investigator assessment
End point description: PFS was defined as the time from the date of randomization to the date of first radiologically documented tumor progression or death from any cause, whichever occurs first. PFS primary analysis performed when 415 events were reached	
End point type	Primary
End point timeframe: Every 6 weeks until disease progression or death which ever occurred first up to 15-Mar-2013	

End point values	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: months				
median (confidence interval 95%)	7 (6.74 to 8.18)	5.78 (5.49 to 6.9)		

Statistical analyses

Statistical analysis title	Comparison of the distribution of PFS
Comparison groups	Everolimus + vinorelbine + trastuzumab v placebo + vinorelbine + trastuzumab
Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0067
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.95

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS was defined as the time from date of randomization to the date of death from any cause. Final OS was conducted when 388 deaths occurred.	
End point type	Secondary
End point timeframe:	
Every 3 months until death up to 1-Apr-2015	

End point values	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: months				
median (confidence interval 95%)	23.46 (20.01 to 28.81)	24.08 (21.49 to 27.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)
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End point description:

ORR was defined as the percentage of participants whose best overall response was either complete response (CR) or partial response (PR) according to RECIST version 1.0

End point type	Secondary
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End point timeframe:

Every 6 weeks until disease progression or death which ever occurred first up to 15-Mar-2013

End point values	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: Percentage of participants				
number (confidence interval 95%)	40.8 (35.1 to 46.8)	37.2 (31.6 to 43.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate (CBR)

End point title	Clinical benefit rate (CBR)
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End point description:

CBR was defined as the percentage of participants whose best overall response, according to RECIST, was either complete response (CR), a partial response (PR) or stable disease (SD) lasting for at least 24 weeks.

End point type	Secondary
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End point timeframe:

Every 6 weeks until disease progression or death which ever occurred first up to 15-Mar-2013

End point values	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: Percentage of participants				
number (confidence interval 95%)	59.2 (53.2 to 64.9)	53.3 (47.4 to 59.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration of the ECOG performance status score

End point title	Time to deterioration of the ECOG performance status score
End point description: The Time to deterioration of the ECOG performance status score was summarized at the time of each assessment.	
End point type	Secondary
End point timeframe: baseline, until disease progression or death up to 15-Mar-2013	

End point values	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: months				
number (not applicable)	32.66	21.55		

Statistical analyses

No statistical analyses for this end point

Secondary: PRO: Time to deterioration in global health status/QoL domain score of the European Organization for the Research and Treatment of Cancer (EORTC)-Core Quality of Life Questionnaire (QLQ-C30) (by at least 10%)

End point title	PRO: Time to deterioration in global health status/QoL domain score of the European Organization for the Research and Treatment of Cancer (EORTC)-Core Quality of Life Questionnaire (QLQ-C30) (by at least 10%)
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End point description:

PRO = patient reported outcomes; Time to deterioration ($\geq 10\%$ worsening from baseline), in the global health status of EORTC QLQ-C30 scale was done in the 3 functional scales (emotional, physical, & social functioning [EF, PF, & SF]). It contains 30 items & is composed of multi-item scales & single-item measures. These include 5 functional scales (physical, role, emotional, social & cognitive functioning), 3 symptom scales (fatigue, pain, nausea, & vomiting), a global health status/QoL scale, and 6 single items (dyspnea, diarrhea, constipation, anorexia, insomnia & financial impact). Each of the multi-item scale

includes a different set of items - no item occurs in more than 1 scale. Each item in the EORTC QLQ-C30 has 4 response categories (1=Not at all, 2= A little, 3= Quite a bit, 4= Very much) with the higher number representing a worse outcome. The global health domain score of the QLQ-C30 questionnaire was pre-specified as the primary QoL domain of interest & disclosed here.

End point type	Secondary
End point timeframe:	
Baseline, until disease progression or death up to 15-Mar-2013	

End point values	Everolimus + vinorelbine + trastuzumab	placebo + vinorelbine + trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	285		
Units: months				
median (confidence interval 95%)				
Deterioration - global QoL domain by at least 10%	8.31 (6.93 to 11.53)	7.29 (5.55 to 10.38)		
Deterioration in the PF domain by at least 10%	11.96 (8.31 to 14.09)	12.48 (8.31 to 20.86)		
Deterioration in the EF domain by at least 10%	15.18 (9.2 to 17.28)	12.45 (9.69 to 16.36)		
Deterioration in the SF domain by at least 10%	11.33 (8.18 to 14.52)	13.11 (8.31 to 19.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Everolimus blood concentrations by leading dose and time point

End point title	Everolimus blood concentrations by leading dose and time point
End point description:	
Pre-dose (Cmin) and 2 hours post-dose (C2h) everolimus PK blood samples were collected at Cycle 2 Day 1. Only valid everolimus PK blood samples collected at steady state were used in the analyses.	
End point type	Secondary
End point timeframe:	
Cycle 2, Day 1	

End point values	Everolimus 2.5 mg	Everolimus 5mg/day		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	43		
Units: ng/ml				
arithmetic mean (standard deviation)				
Pre-dose (Cmin) (n: 7, 32)	2.928 (± 2.6197)	5.652 (± 4.1006)		
2 hours post administration (C2h) (n:10, 43)	13.035 (± 6.6842)	22.005 (± 13.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vinorelbine blood concentrations by leading dose and time point

End point title	Vinorelbine blood concentrations by leading dose and time point
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End point description:

Pre-infusion (Cmin) and end of infusion (C2h) vinorelbine PK blood samples were collected at Cycle 2 Day 1. Only valid vinorelbine PK blood samples collected at steady state were used in the analyses.

End point type	Secondary
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End point timeframe:

Cycle 2, Day 1

End point values	Everolimus (Vinorelbine blood concentration)	Everolimus Placebo (Vinorelbine blood concentration)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	64		
Units: ng/ml				
arithmetic mean (standard deviation)				
Pre-infusion - dose (Cmin) (n: 76, 64)	11.085 (± 66.8551)	0.061 (± 0.4888)		
End of infusion (Cmax) (n: 58, 49)	867.147 (± 971.3057)	1068.51 (± 1145.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trastuzumab blood concentrations by leading dose and time point

End point title	Trastuzumab blood concentrations by leading dose and time point
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End point description:

Pre-infusion (Cmin) and end of infusion (C2h) trastuzumab PK blood samples were collected at Cycle 3 Day 1. Only valid trastuzumab PK blood samples collected at steady state were used in the analyses.

End point type	Secondary
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End point timeframe:

Cycle 3, Day 1

End point values	Everolimus (trastuzumab serum concentration)	Everolimus Placebo (trastuzumab serum concentration)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	59		
Units: ng/ml				
arithmetic mean (standard deviation)				
Pre-infusion - dose (Cmin) (n: 73, 57)	23.351 (± 6.3344)	24.526 (± 7.996)		
End of infusion (Cmax) (n: 75, 59)	64.279 (± 27.8549)	60.576 (± 15.5198)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Everolimus + trastuzumab + vinorelbine
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Reporting group description:

Everolimus + trastuzumab + vinorelbine

Reporting group title	Placebo + trastuzumab + vinorelbine
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Reporting group description:

Placebo + trastuzumab + vinorelbine

Serious adverse events	Everolimus + trastuzumab + vinorelbine	Placebo + trastuzumab + vinorelbine	
Total subjects affected by serious adverse events			
subjects affected / exposed	122 / 280 (43.57%)	58 / 282 (20.57%)	
number of deaths (all causes)	7	7	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 280 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			

subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 280 (0.36%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
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			
Asthenia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chills			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 280 (1.07%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	13 / 280 (4.64%)	5 / 282 (1.77%)	
occurrences causally related to treatment / all	5 / 14	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 280 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cough			

subjects affected / exposed	1 / 280 (0.36%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 280 (1.07%)	3 / 282 (1.06%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	3 / 280 (1.07%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
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 / 280 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 280 (1.07%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 280 (0.36%)	5 / 282 (1.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 280 (0.71%)	3 / 282 (1.06%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 280 (1.07%)	5 / 282 (1.77%)	
occurrences causally related to treatment / all	1 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 280 (0.00%)	3 / 282 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Neutrophil count decreased			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (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			
Fall			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 280 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdural haematoma			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 280 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dizziness			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 280 (0.71%)	3 / 282 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (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	3 / 280 (1.07%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (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	0 / 280 (0.00%)	1 / 282 (0.35%)	
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			
Agranulocytosis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	10 / 280 (3.57%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	22 / 22	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	30 / 280 (10.71%)	4 / 282 (1.42%)	
occurrences causally related to treatment / all	28 / 31	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 280 (1.07%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	12 / 280 (4.29%)	3 / 282 (1.06%)	
occurrences causally related to treatment / all	13 / 14	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	4 / 280 (1.43%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 280 (0.71%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract subcapsular			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (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	1 / 280 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 280 (0.71%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	5 / 280 (1.79%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
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 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 280 (1.07%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	9 / 280 (3.21%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	9 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 280 (1.79%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 280 (0.00%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			

subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (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			
Rash			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 280 (1.07%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (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			
Bone pain			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal pain			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 280 (1.43%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			

subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	3 / 280 (1.07%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (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	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 280 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 280 (0.71%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	8 / 280 (2.86%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	3 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative wound infection			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	3 / 280 (1.07%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 280 (0.36%)	2 / 282 (0.71%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	1 / 280 (0.36%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 280 (0.71%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 280 (0.00%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 280 (0.71%)	1 / 282 (0.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			

subjects affected / exposed	1 / 280 (0.36%)	0 / 282 (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	Everolimus + trastuzumab + vinorelbine	Placebo + trastuzumab + vinorelbine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	280 / 280 (100.00%)	280 / 282 (99.29%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	37 / 280 (13.21%)	26 / 282 (9.22%)	
occurrences (all)	49	46	
Aspartate aminotransferase increased			
subjects affected / exposed	33 / 280 (11.79%)	22 / 282 (7.80%)	
occurrences (all)	49	34	
Ejection fraction decreased			
subjects affected / exposed	17 / 280 (6.07%)	5 / 282 (1.77%)	
occurrences (all)	22	5	
Gamma-glutamyltransferase increased			
subjects affected / exposed	29 / 280 (10.36%)	23 / 282 (8.16%)	
occurrences (all)	34	31	
Haemoglobin decreased			
subjects affected / exposed	22 / 280 (7.86%)	18 / 282 (6.38%)	
occurrences (all)	63	47	
Neutrophil count decreased			
subjects affected / exposed	14 / 280 (5.00%)	8 / 282 (2.84%)	
occurrences (all)	90	32	
Weight decreased			
subjects affected / exposed	83 / 280 (29.64%)	47 / 282 (16.67%)	
occurrences (all)	99	62	
White blood cell count decreased			

subjects affected / exposed occurrences (all)	17 / 280 (6.07%) 104	23 / 282 (8.16%) 112	
Vascular disorders			
Hot flush			
subjects affected / exposed	4 / 280 (1.43%)	16 / 282 (5.67%)	
occurrences (all)	4	16	
Hypertension			
subjects affected / exposed	24 / 280 (8.57%)	10 / 282 (3.55%)	
occurrences (all)	29	12	
Phlebitis			
subjects affected / exposed	14 / 280 (5.00%)	18 / 282 (6.38%)	
occurrences (all)	19	23	
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 280 (11.07%)	24 / 282 (8.51%)	
occurrences (all)	35	30	
Dysgeusia			
subjects affected / exposed	32 / 280 (11.43%)	17 / 282 (6.03%)	
occurrences (all)	37	18	
Headache			
subjects affected / exposed	74 / 280 (26.43%)	62 / 282 (21.99%)	
occurrences (all)	105	98	
Hypoaesthesia			
subjects affected / exposed	15 / 280 (5.36%)	7 / 282 (2.48%)	
occurrences (all)	17	9	
Neuropathy peripheral			
subjects affected / exposed	27 / 280 (9.64%)	41 / 282 (14.54%)	
occurrences (all)	32	47	
Paraesthesia			
subjects affected / exposed	21 / 280 (7.50%)	21 / 282 (7.45%)	
occurrences (all)	27	25	
Peripheral sensory neuropathy			
subjects affected / exposed	25 / 280 (8.93%)	17 / 282 (6.03%)	
occurrences (all)	32	19	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	137 / 280 (48.93%)	85 / 282 (30.14%)	
occurrences (all)	253	182	
Febrile neutropenia			
subjects affected / exposed	17 / 280 (6.07%)	7 / 282 (2.48%)	
occurrences (all)	21	7	
Leukopenia			
subjects affected / exposed	126 / 280 (45.00%)	105 / 282 (37.23%)	
occurrences (all)	509	567	
Neutropenia			
subjects affected / exposed	226 / 280 (80.71%)	196 / 282 (69.50%)	
occurrences (all)	1117	1127	
Thrombocytopenia			
subjects affected / exposed	39 / 280 (13.93%)	6 / 282 (2.13%)	
occurrences (all)	89	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	74 / 280 (26.43%)	57 / 282 (20.21%)	
occurrences (all)	166	100	
Chills			
subjects affected / exposed	18 / 280 (6.43%)	18 / 282 (6.38%)	
occurrences (all)	22	22	
Fatigue			
subjects affected / exposed	124 / 280 (44.29%)	119 / 282 (42.20%)	
occurrences (all)	252	217	
Oedema peripheral			
subjects affected / exposed	39 / 280 (13.93%)	23 / 282 (8.16%)	
occurrences (all)	56	25	
Non-cardiac chest pain			
subjects affected / exposed	11 / 280 (3.93%)	20 / 282 (7.09%)	
occurrences (all)	13	25	
Pyrexia			
subjects affected / exposed	107 / 280 (38.21%)	65 / 282 (23.05%)	
occurrences (all)	181	128	
Pain			

subjects affected / exposed occurrences (all)	20 / 280 (7.14%) 24	20 / 282 (7.09%) 27	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	45 / 280 (16.07%)	52 / 282 (18.44%)	
occurrences (all)	63	69	
Abdominal pain upper			
subjects affected / exposed	34 / 280 (12.14%)	40 / 282 (14.18%)	
occurrences (all)	48	54	
Constipation			
subjects affected / exposed	84 / 280 (30.00%)	88 / 282 (31.21%)	
occurrences (all)	99	121	
Diarrhoea			
subjects affected / exposed	108 / 280 (38.57%)	88 / 282 (31.21%)	
occurrences (all)	200	177	
Dry mouth			
subjects affected / exposed	14 / 280 (5.00%)	7 / 282 (2.48%)	
occurrences (all)	16	10	
Dyspepsia			
subjects affected / exposed	21 / 280 (7.50%)	25 / 282 (8.87%)	
occurrences (all)	28	33	
Mouth ulceration			
subjects affected / exposed	32 / 280 (11.43%)	6 / 282 (2.13%)	
occurrences (all)	68	8	
Nausea			
subjects affected / exposed	98 / 280 (35.00%)	105 / 282 (37.23%)	
occurrences (all)	151	163	
Stomatitis			
subjects affected / exposed	174 / 280 (62.14%)	78 / 282 (27.66%)	
occurrences (all)	412	140	
Vomiting			
subjects affected / exposed	57 / 280 (20.36%)	59 / 282 (20.92%)	
occurrences (all)	88	106	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	84 / 280 (30.00%)	55 / 282 (19.50%)	
occurrences (all)	102	70	
Dyspnoea			
subjects affected / exposed	51 / 280 (18.21%)	40 / 282 (14.18%)	
occurrences (all)	63	50	
Epistaxis			
subjects affected / exposed	64 / 280 (22.86%)	38 / 282 (13.48%)	
occurrences (all)	90	51	
Oropharyngeal pain			
subjects affected / exposed	27 / 280 (9.64%)	27 / 282 (9.57%)	
occurrences (all)	32	33	
Pneumonitis			
subjects affected / exposed	17 / 280 (6.07%)	9 / 282 (3.19%)	
occurrences (all)	19	9	
Rhinorrhoea			
subjects affected / exposed	17 / 280 (6.07%)	14 / 282 (4.96%)	
occurrences (all)	21	17	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	71 / 280 (25.36%)	54 / 282 (19.15%)	
occurrences (all)	105	81	
Pruritus			
subjects affected / exposed	16 / 280 (5.71%)	29 / 282 (10.28%)	
occurrences (all)	30	38	
Alopecia			
subjects affected / exposed	22 / 280 (7.86%)	29 / 282 (10.28%)	
occurrences (all)	24	29	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	13 / 280 (4.64%)	18 / 282 (6.38%)	
occurrences (all)	14	18	
Insomnia			
subjects affected / exposed	34 / 280 (12.14%)	27 / 282 (9.57%)	
occurrences (all)	39	31	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	37 / 280 (13.21%)	46 / 282 (16.31%)	
occurrences (all)	52	59	
Arthralgia			
subjects affected / exposed	48 / 280 (17.14%)	36 / 282 (12.77%)	
occurrences (all)	64	44	
Bone pain			
subjects affected / exposed	28 / 280 (10.00%)	24 / 282 (8.51%)	
occurrences (all)	33	32	
Muscle spasms			
subjects affected / exposed	31 / 280 (11.07%)	47 / 282 (16.67%)	
occurrences (all)	45	69	
Musculoskeletal chest pain			
subjects affected / exposed	16 / 280 (5.71%)	12 / 282 (4.26%)	
occurrences (all)	18	13	
Musculoskeletal pain			
subjects affected / exposed	14 / 280 (5.00%)	14 / 282 (4.96%)	
occurrences (all)	15	15	
Myalgia			
subjects affected / exposed	39 / 280 (13.93%)	31 / 282 (10.99%)	
occurrences (all)	51	42	
Pain in extremity			
subjects affected / exposed	42 / 280 (15.00%)	44 / 282 (15.60%)	
occurrences (all)	51	59	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	37 / 280 (13.21%)	29 / 282 (10.28%)	
occurrences (all)	67	62	
Upper respiratory tract infection			
subjects affected / exposed	38 / 280 (13.57%)	26 / 282 (9.22%)	
occurrences (all)	55	36	
Urinary tract infection			
subjects affected / exposed	26 / 280 (9.29%)	18 / 282 (6.38%)	
occurrences (all)	37	27	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	94 / 280 (33.57%) 131	49 / 282 (17.38%) 60	
Hypercholesterolaemia subjects affected / exposed occurrences (all)	26 / 280 (9.29%) 30	12 / 282 (4.26%) 36	
Hyperglycaemia subjects affected / exposed occurrences (all)	26 / 280 (9.29%) 37	15 / 282 (5.32%) 22	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	23 / 280 (8.21%) 36	9 / 282 (3.19%) 10	
Hypokalaemia subjects affected / exposed occurrences (all)	34 / 280 (12.14%) 62	19 / 282 (6.74%) 24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2010	Amendment 1 introduced the following non-administrative changes and was issued when 16 patients had been randomized: Guidelines regarding the management of HBV and HCV infections were added. Reactivation of HBV has been observed in cancer patients receiving either chemotherapy or
25 January 2011	Amendment 2 was issued when 163 patients had been randomized. The primary purpose of this amendment was to revise exclusion criterion number 4, which had originally excluded all patients with a history of CNS metastases. The amended criterion allowed patients with previously treated CNS metastases to enroll in the study provided that the last treatment received for the CNS metastases was at least 8 weeks prior to randomization, including radiotherapy, steroids and anti-epileptic medication. A total of nine patients with CNS metastases were enrolled in this trial and the time to progression results suggested that everolimus can positively affect CNS disease. Accordingly,
15 May 2013	The key changes for Amendment 3 included the following: conduct and dissemination of OS analyses results to Novartis personnel and health authorities; inclusion of central review for tumor assessment data. Overall survival (OS) is pre-specified as a key secondary endpoint, as per the original protocol, results of OS analysis were not to be communicated to clinical team or any party

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.

cut off date for the Safety data: 1 Apr 2015

Notes: