



Clinical trial results:

A phase Ib/II study investigating the combination of everolimus with trastuzumab and paclitaxel in patients with HER2-overexpressing metastatic breast cancer

Summary

EudraCT number	2006-001596-37
Trial protocol	BE
Global end of trial date	10 April 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CRAD001J2101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00426556
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	10 April 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this phase II study was to evaluate the efficacy of the dose level/regimen of everolimus recommended from the Phase I with trastuzumab and paclitaxel (PT) therapy in patients with HER2-overexpressing metastatic breast cancer whose disease progressed on/after trastuzumab mono- and/or combination therapy based on the evaluation of objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Objective response rate (ORR) was defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR). Only patients with measurable disease (the presence of at least one measurable lesion) at baseline were included in the study. CR = Disappearance of all target lesions; PR = At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters.

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. In addition, the doses and schedules of everolimus investigated in this study were based on previous safety experience in earlier everolimus phase I oncology studies that showed everolimus monotherapy to be pharmacodynamically active and satisfactorily tolerated in two different regimens-weekly at doses of 50 to 70 mg and daily at doses of 5 and 10 mg.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 51
Worldwide total number of subjects	88
EEA total number of subjects	61

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)	71
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Based on the results of the Phase I portion of this study, in addition to all available information on daily and weekly everolimus regimen in breast cancer and other tumors, all patients in the Phase II portion of the study were allocated to one arm to receive the recommended everolimus dose of 10 mg daily in combination with PT.

Period 1

Period 1 title	Phase I and Phase II Core Phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	RAD001 5mg + PT, Daily
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Arm description:

Daily dosing schedule of everolimus 5 mg plus weekly paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab

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:

Patients received 5 mg everolimus once daily.

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

Dosage and administration details:

Paclitaxel was administered weekly in a 28-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered weekly in a 28-day cycle.

Arm title	RAD001 10 mg + PT, Daily
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Arm description:

Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab

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

Dosage and administration details:

Patients received 10 mg everolimus once daily.

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

Dosage and administration details:

Paclitaxel was administered weekly in a 28-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered weekly in a 28-day cycle.

Arm title	RAD001 30 mg + PT, Weekly
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Arm description:

Weekly dosing schedule of everolimus 30 mg plus paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab.

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:

Patients received 30 mg everolimus once daily.

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

Dosage and administration details:

Paclitaxel was administered weekly in a 28-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered weekly in a 28-day cycle.

Arm title	RAD001 10 mg + PT, Daily (Phase 2)
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Arm description:

Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = Paclitaxel and Trastuzumab

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

Dosage and administration details:

Patients received 10 mg everolimus once daily.

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

Dosage and administration details:

Paclitaxel was administered weekly in a 28-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered weekly in a 28-day cycle.

Number of subjects in period 1	RAD001 5mg + PT, Daily	RAD001 10 mg + PT, Daily	RAD001 30 mg + PT, Weekly
Started	6	17	10
Completed	5	7	7
Not completed	1	10	3
Consent withdrawn by subject	-	-	-
Adverse Event	1	3	1
Death	-	1	-
Disease Progression	-	6	2

Number of subjects in period 1	RAD001 10 mg + PT, Daily (Phase 2)
Started	55
Completed	28
Not completed	27
Consent withdrawn by subject	3
Adverse Event	8
Death	-
Disease Progression	16

Period 2

Period 2 title	Phase I and Phase II Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RAD001 5 mg + PT, Daily

Arm description:

Daily dosing schedule of everolimus 5 mg plus weekly paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab

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:

Patients received 5 mg everolimus once daily.

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

Dosage and administration details:

Paclitaxel was administered weekly in a 28-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered weekly in a 28-day cycle.

Arm title	RAD001 10 mg + PT, Daily
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Arm description:

Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = Paclitaxel and Trastuzumab

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:

Patients received 10 mg everolimus once daily.

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

Dosage and administration details:	
Paclitaxel was administered weekly in a 28-day cycle.	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Trastuzumab was administered weekly in a 28-day cycle.	
Arm title	RAD001 30 mg + PT, Weekly
Arm description:	
Weekly dosing schedule of everolimus 30 mg plus paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab.	
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:	
Patients received 30 mg everolimus once daily.	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Paclitaxel was administered weekly in a 28-day cycle.	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Trastuzumab was administered weekly in a 28-day cycle.	
Arm title	RAD001 10 mg + PT, Daily (Phase 2)
Arm description:	
Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = Paclitaxel and Trastuzumab	
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:	
Patients received 10 mg everolimus once daily.	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered weekly in a 28-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered weekly in a 28-day cycle.

Number of subjects in period 2^[1]	RAD001 5 mg + PT, Daily	RAD001 10 mg + PT, Daily	RAD001 30 mg + PT, Weekly
Started	5	7	7
Completed	0	1	0
Not completed	5	6	7
Adverse Event	-	1	1
Disease Progression	5	5	6

Number of subjects in period 2^[1]	RAD001 10 mg + PT, Daily (Phase 2)
Started	24
Completed	1
Not completed	23
Adverse Event	2
Disease Progression	21

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of the 28 patients in RAD001 10 mg+ PT, daily (Phase 2) that completed Phase I, 4 patients did not enter the Phase II Extension Phase.

Baseline characteristics

Reporting groups

Reporting group title	RAD001 5mg + PT, Daily
Reporting group description: Daily dosing schedule of everolimus 5 mg plus weekly paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab	
Reporting group title	RAD001 10 mg + PT, Daily
Reporting group description: Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab	
Reporting group title	RAD001 30 mg + PT, Weekly
Reporting group description: Weekly dosing schedule of everolimus 30 mg plus paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab.	
Reporting group title	RAD001 10 mg + PT, Daily (Phase 2)
Reporting group description: Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = Paclitaxel and Trastuzumab	

Reporting group values	RAD001 5mg + PT, Daily	RAD001 10 mg + PT, Daily	RAD001 30 mg + PT, Weekly
Number of subjects	6	17	10
Age categorical			
Units: Subjects			
< 65	6	13	6
>= 65	0	4	4
Gender categorical			
Units: Subjects			
Female	6	17	10
WHO Performance Status			
0=Fully active, able to carry out normal activity without restriction, 1=Restricted in physical strenuous activity but ambulatory and able to carry work of a light or sedentary nature e.g. light house work, office work.			
Units: Subjects			
PS=0	4	5	4
PS=1	2	12	6

Reporting group values	RAD001 10 mg + PT, Daily (Phase 2)	Total	
Number of subjects	55	88	
Age categorical			
Units: Subjects			
< 65	46	71	
>= 65	9	17	
Gender categorical			
Units: Subjects			
Female	55	88	
WHO Performance Status			
0=Fully active, able to carry out normal activity without restriction, 1=Restricted in physical strenuous activity but ambulatory and able to carry work of a light or sedentary nature e.g. light house work, office work.			

Units: Subjects			
PS=0	36	49	
PS=1	19	39	

End points

End points reporting groups

Reporting group title	RAD001 5mg + PT, Daily
Reporting group description: Daily dosing schedule of everolimus 5 mg plus weekly paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab	
Reporting group title	RAD001 10 mg + PT, Daily
Reporting group description: Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab	
Reporting group title	RAD001 30 mg + PT, Weekly
Reporting group description: Weekly dosing schedule of everolimus 30 mg plus paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab.	
Reporting group title	RAD001 10 mg + PT, Daily (Phase 2)
Reporting group description: Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = Paclitaxel and Trastuzumab	
Reporting group title	RAD001 5 mg + PT, Daily
Reporting group description: Daily dosing schedule of everolimus 5 mg plus weekly paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab	
Reporting group title	RAD001 10 mg + PT, Daily
Reporting group description: Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = Paclitaxel and Trastuzumab	
Reporting group title	RAD001 30 mg + PT, Weekly
Reporting group description: Weekly dosing schedule of everolimus 30 mg plus paclitaxel plus trastuzumab. PT = paclitaxel and trastuzumab.	
Reporting group title	RAD001 10 mg + PT, Daily (Phase 2)
Reporting group description: Daily dosing schedule of everolimus 10 mg plus weekly paclitaxel plus trastuzumab. PT = Paclitaxel and Trastuzumab	

Primary: Overall Response Rate: RAD001 10 mg + PT, Daily (Phase 2)

End point title	Overall Response Rate: RAD001 10 mg + PT, Daily (Phase
End point description: The primary objective in Phase II was to evaluate efficacy of the dose level/regimen of everolimus from Phase I with PT therapy in patients with HER2-overexpressing metastatic breast cancer whose disease progressed on/after trastuzumab mono-and/or combination therapy based on evaluation of objective response rate (ORR: defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) per RECIST). Only patients with measurable disease (the presence of at least one measurable lesion) at baseline were included in the study. CR = Disappearance of all target lesions; PR = At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters. This included the Full Analysis Set, which consisted of all patients who received a least one dose of any one compound of study treatment. Patients were analyzed according to the everolimus dose level to which they enrolled.	
End point type	Primary
End point timeframe: Every 8 to 9 weeks.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: A Simon two-stage design was used to assess the efficacy of the recommended dose. This design provides rules for a decision to be based on number of responders observed either to stop or to proceed with the second stage. Responses were summarized in terms of percentage rates along with exact 2-sided 95% confidence intervals. The Clopper-Pearson method was used to determine the confidence intervals.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only RAD001 10 mg + PT, Daily (Phase 2) was included in this analysis.

End point values	RAD001 10 mg + PT, Daily (Phase 2)			
Subject group type	Reporting group			
Number of subjects analysed	55 ^[3]			
Units: Percentage of Participants				
number (not applicable)				
Objective Response Rate	21.8			

Notes:

[3] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response

End point title	Best Overall Response ^[4]
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End point description:

Best overall response rate (BOR) was determined based on investigator assessment of overall lesion response using RECIST criteria guidelines. BOR = objective responses rate (ORR), disease control rate (DCR) or clinical benefit rate (CBR). ORR = (complete response (CR) or partial response (PR)); DCR = (CR or PR or Stable disease (SD)); CBR = (CR or PR or SD $\geq$ 24 weeks). CR = Disappearance of all target lesions; PR = At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters; SD = Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for partial disease (PD). PD = At least a 20% increase in the sum of the longest diameter of all measured target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or after baseline.

End point type	Secondary
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End point timeframe:

Every 8 to 9 weeks .

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: RAD001 10 mg + PT, Daily (Phase 2) was not included in this analysis.

End point values	RAD001 5mg + PT, Daily	RAD001 10 mg + PT, Daily	RAD001 30 mg + PT, Weekly	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[5]	17 ^[6]	10 ^[7]	
Units: Percentage of Participants				
number (not applicable)				
Objective Response Rate (ORR)	83.3	23.5	30	
Disease Control Rate (DCR)	83.3	82.4	80	
Clinical Benefit Rate (CBR)	83.3	47.1	70	

Notes:

[5] - Full analysis set

[6] - Full analysis set

[7] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS): RAD001 10 mg + PT, Daily (Phase 2)

End point title	Progression Free Survival (PFS): RAD001 10 mg + PT, Daily (Phase 2) ^[8]
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End point description:

PFS is defined as the time from start of treatment to the date of first documented progression or death due to any cause. If a patient has not had an event, PFS will be censored at the date of last adequate tumor assessment. The Full Analysis Set was used, which consisted of all patients who received a least one dose of any one compound of the study treatment. Patients were analyzed according to the everolimus dose level to which they enrolled.

End point type	Secondary
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End point timeframe:

Every 8 to 9 weeks.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only RAD001 10 mg + PT, Daily (Phase 2) was included in this analysis.

End point values	RAD001 10 mg + PT, Daily (Phase 2)			
Subject group type	Reporting group			
Number of subjects analysed	55 ^[9]			
Units: Months				
median (confidence interval 95%)				
Progression Free Survival (PFS)	5.52 (4.99 to 7.69)			

Notes:

[9] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS): RAD001 10 mg + PT, Daily (Phase 2)

End point title	Overall Survival (OS): RAD001 10 mg + PT, Daily (Phase 2) ^[10]
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End point description:

Overall survival (OS) is defined as the time from start of treatment to the date of death due to any cause. If a patient is not known to have died, survival was censored at the last date of contact. OS was to be reported at extension and after 3-year follow-up. The Kaplan-Meier median was used to analyze the OS. The Full Analysis Set (FAS) was used, which consisted of all patients who received a least one dose of any one compound of the study treatment. Patients were analyzed according to the everolimus dose level to which they enrolled.

End point type	Secondary
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End point timeframe:

Every 3 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only RAD001 10 mg + PT, Daily (Phase 2) was included in this analysis.

End point values	RAD001 10 mg + PT, Daily (Phase 2)			
Subject group type	Reporting group			
Number of subjects analysed	55 ^[11]			
Units: Months				
median (confidence interval 95%)				
Phase II: Overall Survival (OS)	18.07 (12.85 to 24.11)			

Notes:

[11] - Full analysis set

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 are reported in this record from 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
Dictionary version	16.1

Reporting groups

Reporting group title	Phase I - Everolimus 5mg Daily + HT
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Reporting group description:

Phase I - Everolimus 5mg Daily + HT

Reporting group title	Phase II - Everolimus 10mg Daily + HT
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Reporting group description:

Phase II - Everolimus 10mg Daily + HT

Reporting group title	Phase I - Everolimus 30mg Weekly + HT
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Reporting group description:

Phase I - Everolimus 30mg Weekly + HT

Reporting group title	Phase I - Everolimus 10mg Daily + HT
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Reporting group description:

Phase I - Everolimus 10mg Daily + HT

Serious adverse events	Phase I - Everolimus 5mg Daily + HT	Phase II - Everolimus 10mg Daily + HT	Phase I - Everolimus 30mg Weekly + HT
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	26 / 55 (47.27%)	7 / 10 (70.00%)
number of deaths (all causes)	1	3	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	6 / 55 (10.91%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	3 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Alveolitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal obstruction extrinsic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			

subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	4 / 55 (7.27%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	3 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin haemorrhage			

subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monarthrititis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Cell death			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitamin D deficiency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase I - Everolimus 10mg Daily + HT		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphoedema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Alveolitis allergic			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tracheal obstruction extrinsic			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Confusional state			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coma			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Impaired gastric emptying			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pruritus			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Monarthritis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Endocarditis				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasopharyngitis				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 17 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vitamin D deficiency			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase I - Everolimus 5mg Daily + HT	Phase II - Everolimus 10mg Daily + HT	Phase I - Everolimus 30mg Weekly + HT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	55 / 55 (100.00%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cancer pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Ear neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Arterial thrombosis limb			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Lymphoedema			
subjects affected / exposed	1 / 6 (16.67%)	5 / 55 (9.09%)	1 / 10 (10.00%)
occurrences (all)	2	5	1
General disorders and administration site conditions			

Adverse drug reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	4 / 6 (66.67%)	28 / 55 (50.91%)	6 / 10 (60.00%)
occurrences (all)	11	52	12
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Chills			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Face oedema			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Facial pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	12 / 55 (21.82%)	3 / 10 (30.00%)
occurrences (all)	2	15	3
Gait disturbance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Injection site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 10 (0.00%)
occurrences (all)	0	3	0

Oedema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 1	0 / 10 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	13 / 55 (23.64%) 21	3 / 10 (30.00%) 4
Xerosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	0 / 10 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 7	19 / 55 (34.55%) 25	1 / 10 (10.00%) 1
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 2	1 / 10 (10.00%) 1
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 1	0 / 10 (0.00%) 0
Genital discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	0 / 10 (0.00%) 0
Metrorrhagia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 1	0 / 10 (0.00%) 0
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	0 / 10 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	20 / 55 (36.36%) 27	2 / 10 (20.00%) 3
Dysphonia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 55 (5.45%) 3	1 / 10 (10.00%) 1

Dyspnoea			
subjects affected / exposed	2 / 6 (33.33%)	9 / 55 (16.36%)	2 / 10 (20.00%)
occurrences (all)	2	9	6
Epistaxis			
subjects affected / exposed	3 / 6 (50.00%)	16 / 55 (29.09%)	3 / 10 (30.00%)
occurrences (all)	6	29	3
Hypoxia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Larynx irritation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lung disorder			
subjects affected / exposed	1 / 6 (16.67%)	3 / 55 (5.45%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Nasal dryness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Obstructive airways disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	6 / 55 (10.91%)	1 / 10 (10.00%)
occurrences (all)	0	8	1
Pharyngeal ulceration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	2 / 6 (33.33%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 1	0 / 10 (0.00%) 0
Sinus congestion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	0 / 10 (0.00%) 0
Tracheal pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	0 / 10 (0.00%) 0
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	0 / 10 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 55 (1.82%) 1	0 / 10 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 1	0 / 10 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	6 / 55 (10.91%) 6	2 / 10 (20.00%) 2
Mood altered subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 1	1 / 10 (10.00%) 1
Sleep disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	1 / 10 (10.00%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	2 / 55 (3.64%) 4	1 / 10 (10.00%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	3 / 55 (5.45%) 5	0 / 10 (0.00%) 0
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood magnesium decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood phosphorus decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
Blood potassium decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
Carbon monoxide diffusing capacity decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Echography abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	1	3	1
Electrocardiogram abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Haemoglobin decreased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Troponin I increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	2 / 6 (33.33%)	11 / 55 (20.00%)	2 / 10 (20.00%)
occurrences (all)	2	15	2
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	10
Injury, poisoning and procedural complications			
Pubis fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Radiation pneumonitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pericardial effusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Tachycardia			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 1	0 / 10 (0.00%) 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	4 / 55 (7.27%)	0 / 10 (0.00%)
occurrences (all)	0	5	0
Dysaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 55 (7.27%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	23 / 55 (41.82%)	3 / 10 (30.00%)
occurrences (all)	1	39	6
Horner's syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Hypokinesia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Neurotoxicity			
subjects affected / exposed	1 / 6 (16.67%)	6 / 55 (10.91%)	0 / 10 (0.00%)
occurrences (all)	2	8	0
Neuropathy peripheral			
subjects affected / exposed	1 / 6 (16.67%)	20 / 55 (36.36%)	1 / 10 (10.00%)
occurrences (all)	1	22	1
Paraesthesia			
subjects affected / exposed	2 / 6 (33.33%)	6 / 55 (10.91%)	4 / 10 (40.00%)
occurrences (all)	4	10	4
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	1 / 10 (10.00%)
occurrences (all)	0	4	1

Sciatica			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Sinus headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 6 (83.33%)	19 / 55 (34.55%)	4 / 10 (40.00%)
occurrences (all)	11	29	5
Anaemia macrocytic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Febrile neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Leukopenia			
subjects affected / exposed	2 / 6 (33.33%)	12 / 55 (21.82%)	2 / 10 (20.00%)
occurrences (all)	2	20	2
Lymphopenia			
subjects affected / exposed	2 / 6 (33.33%)	11 / 55 (20.00%)	5 / 10 (50.00%)
occurrences (all)	4	18	27
Microcytosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	4 / 6 (66.67%)	20 / 55 (36.36%)	5 / 10 (50.00%)
occurrences (all)	11	32	13
Thrombocytopenia			
subjects affected / exposed	1 / 6 (16.67%)	9 / 55 (16.36%)	0 / 10 (0.00%)
occurrences (all)	1	16	0
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Tinnitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Eye inflammation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 6 (50.00%)	8 / 55 (14.55%)	2 / 10 (20.00%)
occurrences (all)	3	12	4
Abdominal pain lower			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Aphthous stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	9 / 55 (16.36%)	0 / 10 (0.00%)
occurrences (all)	0	11	0
Ascites			

subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	5 / 55 (9.09%)	0 / 10 (0.00%)
occurrences (all)	2	5	0
Constipation			
subjects affected / exposed	2 / 6 (33.33%)	13 / 55 (23.64%)	5 / 10 (50.00%)
occurrences (all)	5	15	6
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)	30 / 55 (54.55%)	7 / 10 (70.00%)
occurrences (all)	14	69	10
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
Dyspepsia			
subjects affected / exposed	3 / 6 (50.00%)	4 / 55 (7.27%)	1 / 10 (10.00%)
occurrences (all)	3	6	2
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal toxicity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Gingival hypertrophy			

subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	21 / 55 (38.18%)	5 / 10 (50.00%)
occurrences (all)	7	31	15
Odynophagia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oral disorder			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Stomatitis			
subjects affected / exposed	3 / 6 (50.00%)	42 / 55 (76.36%)	8 / 10 (80.00%)
occurrences (all)	14	84	22
Tooth loss			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 6 (33.33%)	12 / 55 (21.82%)	4 / 10 (40.00%)
occurrences (all)	12	16	12
Hepatobiliary disorders			

Hepatic steatosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cytolytic hepatitis			
subjects affected / exposed	2 / 6 (33.33%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	2	3	1
Hepatomegaly			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	4 / 6 (66.67%)	15 / 55 (27.27%)	5 / 10 (50.00%)
occurrences (all)	5	16	5
Dermatitis acneiform			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	3 / 6 (50.00%)	6 / 55 (10.91%)	2 / 10 (20.00%)
occurrences (all)	3	8	2
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	10 / 55 (18.18%)	2 / 10 (20.00%)
occurrences (all)	0	12	2
Hyperkeratosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nail disorder			
subjects affected / exposed	2 / 6 (33.33%)	6 / 55 (10.91%)	0 / 10 (0.00%)
occurrences (all)	2	7	0
Nail toxicity			

subjects affected / exposed	0 / 6 (0.00%)	6 / 55 (10.91%)	1 / 10 (10.00%)
occurrences (all)	0	9	1
Onycholysis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Onychomadesis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pigmentation disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	5 / 55 (9.09%)	2 / 10 (20.00%)
occurrences (all)	0	5	7
Rash			
subjects affected / exposed	2 / 6 (33.33%)	26 / 55 (47.27%)	3 / 10 (30.00%)
occurrences (all)	3	36	3
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash vesicular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin mass			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Skin toxicity subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	4 / 55 (7.27%) 4	0 / 10 (0.00%) 0
Skin ulcer subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	1 / 10 (10.00%) 1
Urticaria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 55 (5.45%) 3	0 / 10 (0.00%) 0
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 55 (3.64%) 2	1 / 10 (10.00%) 1
Haematuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	3 / 55 (5.45%) 3	0 / 10 (0.00%) 0
Pollakiuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 55 (1.82%) 1	1 / 10 (10.00%) 1
Proteinuria subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 55 (1.82%) 2	0 / 10 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 55 (0.00%) 0	0 / 10 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	10 / 55 (18.18%) 11	2 / 10 (20.00%) 3
Back pain subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	7 / 55 (12.73%) 7	1 / 10 (10.00%) 1
Bone pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 55 (0.00%) 0	0 / 10 (0.00%) 0

Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	8 / 55 (14.55%)	0 / 10 (0.00%)
occurrences (all)	0	8	0
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Myalgia			
subjects affected / exposed	4 / 6 (66.67%)	10 / 55 (18.18%)	1 / 10 (10.00%)
occurrences (all)	6	12	1
Musculoskeletal pain			
subjects affected / exposed	1 / 6 (16.67%)	9 / 55 (16.36%)	1 / 10 (10.00%)
occurrences (all)	1	10	1
Neck pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	4 / 55 (7.27%)	0 / 10 (0.00%)
occurrences (all)	0	5	0
Tendon pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Clostridial infection			

subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	2 / 10 (20.00%)
occurrences (all)	1	1	4
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Ear infection			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Erysipelas			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Escherichia urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Genital herpes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Helicobacter infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Influenza			

subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Localised infection			
subjects affected / exposed	0 / 6 (0.00%)	4 / 55 (7.27%)	0 / 10 (0.00%)
occurrences (all)	0	4	0
Lymphangitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	10 / 55 (18.18%)	0 / 10 (0.00%)
occurrences (all)	2	11	0
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	5 / 55 (9.09%)	0 / 10 (0.00%)
occurrences (all)	0	6	0
Oral infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	4 / 55 (7.27%)	0 / 10 (0.00%)
occurrences (all)	1	6	0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	3 / 6 (50.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	4	1	0
Sinusitis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	1 / 6 (16.67%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	4 / 55 (7.27%)	0 / 10 (0.00%)
occurrences (all)	1	7	0
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	10 / 55 (18.18%)	1 / 10 (10.00%)
occurrences (all)	1	11	2
Vaginal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Wound infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	2 / 6 (33.33%)	10 / 55 (18.18%)	3 / 10 (30.00%)
occurrences (all)	4	13	3
Diabetes mellitus			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	0 / 10 (0.00%)
occurrences (all)	0	2	0

Dyslipidaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 55 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Electrolyte imbalance			
subjects affected / exposed	0 / 6 (0.00%)	0 / 55 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 55 (5.45%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 55 (3.64%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	7 / 55 (12.73%)	1 / 10 (10.00%)
occurrences (all)	1	12	7
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 55 (1.82%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypophosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	4 / 55 (7.27%)	0 / 10 (0.00%)
occurrences (all)	0	4	0

Non-serious adverse events	Phase I - Everolimus 10mg Daily + HT		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Breast cancer subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Cancer pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Ear neoplasm subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Vascular disorders Arterial thrombosis limb subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Hot flush subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Hypertension subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Lymphoedema subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 4		
General disorders and administration site conditions Adverse drug reaction subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Asthenia subjects affected / exposed occurrences (all)	8 / 17 (47.06%) 12		
Chest pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Chills subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Face oedema			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Facial pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	5		
Gait disturbance			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
General physical health deterioration			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	11 / 17 (64.71%)		
occurrences (all)	15		
Xerosis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	8		
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all) Genital discomfort subjects affected / exposed occurrences (all) Metrorrhagia subjects affected / exposed occurrences (all) Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Hypoxia subjects affected / exposed occurrences (all) Larynx irritation subjects affected / exposed occurrences (all) Lung disorder	6 / 17 (35.29%) 8 3 / 17 (17.65%) 3 6 / 17 (35.29%) 7 11 / 17 (64.71%) 14 1 / 17 (5.88%) 2 1 / 17 (5.88%) 1 1		

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nasal dryness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Obstructive airways disorder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Pharyngeal ulceration			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Sinus congestion			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Tracheal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Confusional state			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Mood altered			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood magnesium decreased			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Blood phosphorus decreased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Blood potassium decreased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Carbon monoxide diffusing capacity decreased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Echography abnormal			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Ejection fraction decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Electrocardiogram abnormal			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Troponin I increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	7		
Weight increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Injury, poisoning and procedural complications			
Pubis fracture subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Radiation pneumonitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Cardiac disorders			
Arrhythmia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Palpitations subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Pericardial effusion subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Tachycardia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3		
Dysaesthesia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Headache subjects affected / exposed occurrences (all)	7 / 17 (41.18%) 14		

Horner's syndrome			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hypokinesia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Neurotoxicity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	9		
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Sciatica			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Sinus headache			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	10		
Anaemia macrocytic			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Febrile neutropenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	9 / 17 (52.94%)		
occurrences (all)	21		
Lymphopenia			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	16		
Microcytosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	12 / 17 (70.59%)		
occurrences (all)	42		
Thrombocytopenia			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	4		
Tinnitus			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Dry eye			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Eye inflammation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	4		
Abdominal pain lower			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Aphthous stomatitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Ascites			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	8 / 17 (47.06%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	11 / 17 (64.71%)		
occurrences (all)	18		
Dental caries			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Dysphagia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gastrointestinal toxicity			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Gingival hypertrophy			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gingival pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Gingivitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Nausea			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	10		
Odynophagia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oral disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	16 / 17 (94.12%)		
occurrences (all)	33		
Tooth loss			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	7		
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Cytolytic hepatitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hepatomegaly			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Alopecia			

subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	6		
Dermatitis acneiform			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Hyperkeratosis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nail disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nail toxicity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Onycholysis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Onychomadesis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pigmentation disorder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Pruritus			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	8 / 17 (47.06%)		
occurrences (all)	11		
Rash maculo-papular			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rash vesicular			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin exfoliation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin mass			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin toxicity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Haematuria			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	6		
Back pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Musculoskeletal pain			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Tendon pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
Candidiasis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Clostridial infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Device related infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Erysipelas			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Escherichia urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	5		
Gastroenteritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Genital herpes			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Helicobacter infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Herpes simplex			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Lymphangitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		

Oral infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	7		
Sinusitis			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Skin infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Subcutaneous abscess			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		

Vaginal infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Decreased appetite			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	7		
Diabetes mellitus			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dyslipidaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Electrolyte imbalance			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hypercholesterolaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Hypertriglyceridaemia			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Hypophosphataemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2007	The PK sampling for paclitaxel was changed based on data from the [CRAD001C2104] study.No statistically significant interaction could be shown between the two drugs for Tmax, Cmax and AUClast. In the present study, everolimus could have been administered once-weekly at doses ranging from 30 mg to 50 mg and if feasible, as high as 70 mg. Potential for the effect of everolimus on paclitaxel at higher doses could not be excluded. It was decided that a full paclitaxel pharmacokinetic profile, assessed in a subset of patients receiving the drug combination, would best address the objective to assess the effect of everolimus on systemic plasma exposure of paclitaxel. The collection of trough plasma concentrations of paclitaxel in the present study was removed from the protocol and paclitaxel pharmacokinetic profile assessment at higher dose levels of everolimus was added. Paclitaxel samples were to be collected in at least four patients.Clarifications regarding the washout period for endocrine treatment and lapatinib received prior to study start were added to the exclusion criteria. Inclusion/Exclusion criteria regarding previous taxane therapy for advanced disease were adapted to reflect current treatment practice. Slight changes to blood collection for analysis procedures were made. Novartis RECIST guideline was replaced by: Guidelines for Response, Duration of Overall Response, Time to Treatment Failure (TTF), Time to Progression (TTP), Progression-Free Survival and Overall Survival (based on RECIST).
11 March 2008	A phase II component was added to the study to evaluate the efficacy of the recommended dose levels/regimens of everolimus with trastuzumab and paclitaxel therapy as determined in the phase I part of the trial. Some other changes were: •Some clarifications, as well as changes to improve consistency, were made to dose modifications due to AEs. •The use of any paclitaxel provided by any manufacturer, instead of only Taxol®, was permitted, where applicable, considering local regulations and practices. •Unscheduled pharmacokinetic sampling; on the day of scheduled PK sampling the dose of the relevant study drug was missed, was clarified. •Pharmacokinetic parameters determined from plasma concentration-time profiles were added or clarified. •An additional sampling time point for plasma markers of angiogenesis (VEGF, bFGF) were added at the EOT visit.
14 August 2009	Enrollment was closed on 31 October 2008; 33 patients were enrolled and treated (6 patients in the 5 mg daily schedule, 17 patients in the 10 mg daily schedule and 10 patients in the 30 mg weekly schedule). From the last dose decision teleconference (31-Sept-2008), the study team and investigators concluded that 10 mg daily dose of everolimus in combination with trastuzumab and paclitaxel presented the most favorable risk/benefit profile for this patient population and therefore would be evaluated in the phase II part of the study: everolimus 10 mg daily in combination with trastuzumab and paclitaxel.
07 May 2010	Reactivation of hepatitis B (HBV) was observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of hepatitis B virus reactivation and associated morbidity and mortality (Loomba et al 2008). Guidance was added regarding the identification of patients at risk of hepatitis B, providing prophylactic treatment to them prior to and throughout the duration of everolimus therapy, and monitoring them for reactivation of HBV. Guidance on the management of patients at risk of hepatitis C viral reactivation was also provided.

25 March 2013	Redefine the follow-up survival period for Phase II. Per the original definition, patients are to be followed for survival every 3 months until death or lost to follow-up, up to 3 years after last patient's EOT (i.e. last patient's last date of study treatment) whichever is later. Per this amendment, patients will be followed for survival up to 3 years after last patient's first visit. This newly defined follow-up period when implemented will shorten the follow-up period by approximately 2 years and will only apply to 9 patients or less who are being followed at that time.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported