Clinical trial results:
A Two-Part, Adaptive, Randomized Trial of Ridaforolimus in Combination with Dalotuzumab Compared to Exemestane or Compared to Ridaforolimus or Dalotuzumab Monotherapy in Estrogen Receptor Positive Breast Cancer Patients (MK-8669-041)

Summary

EudraCT number	2010-019867-13
Trial protocol	ES DE IE BE DK SE FR IT GB
Global end of trial date	15 October 2013

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	24 June 2015

Trial information

Trial identification

Sponsor protocol code	8669-041

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01234857
WHO universal trial number (UTN)	-
Other trial identifiers	MK-8669-041: Merck Study Number

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@Merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@Merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2013
Global end of trial reached?	Yes
Global end of trial date	15 October 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is a two-part study that will determine, if 1.) the combination of ridaforolimus and dalotuzumab will improve progression free survival (PFS) compared to exemestane; and 2.) the combination of ridaforolimus and dalotuzumab will improve PFS compared to both ridaforolimus and dalotuzumab as single agents, in participants with estrogen receptor (ER)-positive breast cancer.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	115
EEA total number of subjects	58

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)	75
From 65 to 84 years	39
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants must have had metastatic or locally advanced breast cancer, must have received at least one line of endocrine therapy, and must have been ER-positive and human epidermal growth factor 2 (HER-2) negative, with a life expectancy of at least 3 months.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ridaforolimus 30 mg + dalotuzumab 10 mg

Arm description:

Participants receive ridaforolimus 30 mg orally (PO) on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg intravenously (IV) on Days 1, 8, 15, & 22 of each 28-day cycle.

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

Dosage and administration details:

Ridaforolimus enteric-coated tablets taken orally at assigned dose according to study arm assignment.

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

Dosage and administration details:

Dalotuzumab 10 mg/kg (weight-based dosing) administered IV.

Arm title	Exemestane 25 mg

Arm description:

Participants receive exemestane 25 mg PO once per day (QD).

Arm type	Active comparator
Investigational medicinal product name	exemestane
Investigational medicinal product code	
Other name	AROMASIN(R)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25 mg tablet QD.

Arm title	Ridaforolimus 20 mg + dalotuzumab 10 mg

Arm description:

Participants receive ridaforolimus 20 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10

mg/kg intravenously IV on Days 1, 8, 15, & 22 of each 28-day cycle.

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

Dosage and administration details:

Ridaforolimus enteric-coated tablets taken orally at assigned dose according to study arm assignment.

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

Dosage and administration details:

Dalotuzumab 10 mg/kg (weight-based dosing) administered IV.

Arm title	Ridaforolimus 10 mg + dalotuzumab 10 mg

Arm description:

Participants receive ridaforolimus 10 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg IV on Days 1, 8, 15, & 22 of each 28-day cycle.

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

Dosage and administration details:

Ridaforolimus enteric-coated tablets taken orally at assigned dose according to study arm assignment.

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

Dosage and administration details:

Dalotuzumab 10 mg/kg (weight-based dosing) administered IV.

Number of subjects in period 1	Ridaforolimus 30 mg + dalotuzumab 10 mg	Exemestane 25 mg	Ridaforolimus 20 mg + dalotuzumab 10 mg
Started	29	33	27
Completed	0	0	0
Not completed	29	33	27
Adverse event, serious fatal	1	1	1
Physician decision	2	1	2
Consent withdrawn by subject	3	5	-
Adverse event, non-fatal	8	5	4
Lack of efficacy	15	20	20

Protocol deviation	-	1	-

Number of subjects in period 1	Ridaforolimus 10 mg + dalotuzumab 10 mg
Started	26
Completed	0
Not completed	26
Adverse event, serious fatal	-
Physician decision	6
Consent withdrawn by subject	4
Adverse event, non-fatal	3
Lack of efficacy	13
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Ridaforolimus 30 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 30 mg orally (PO) on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg intravenously (IV) on Days 1, 8, 15, & 22 of each 28-day cycle.	
Reporting group title	Exemestane 25 mg
Reporting group description:	
Participants receive exemestane 25 mg PO once per day (QD).	
Reporting group title	Ridaforolimus 20 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 20 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg intravenously IV on Days 1, 8, 15, & 22 of each 28-day cycle.	
Reporting group title	Ridaforolimus 10 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 10 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg IV on Days 1, 8, 15, & 22 of each 28-day cycle.	

Reporting group values	Ridaforolimus 30 mg + dalotuzumab 10 mg	Exemestane 25 mg	Ridaforolimus 20 mg + dalotuzumab 10 mg
Number of subjects	29	33	27
Age categorical			
Units: Subjects			
Adults (18-64 years)	18	21	19
From 65-84 years	11	12	8
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	60.3	62.4	58.1
standard deviation	± 11.9	± 9.3	± 11.6
Gender categorical			
Units: Subjects			
Female	29	33	27
Male	0	0	0

Reporting group values	Ridaforolimus 10 mg + dalotuzumab 10 mg	Total	
Number of subjects	26	115	
Age categorical			
Units: Subjects			
Adults (18-64 years)	17	75	
From 65-84 years	8	39	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	61.5		
standard deviation	± 11.8	-	

Gender categorical Units: Subjects			
Female	26	115	
Male	0	0	

End points

End points reporting groups

Reporting group title	Ridaforolimus 30 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 30 mg orally (PO) on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg intravenously (IV) on Days 1, 8, 15, & 22 of each 28-day cycle.	
Reporting group title	Exemestane 25 mg
Reporting group description:	
Participants receive exemestane 25 mg PO once per day (QD).	
Reporting group title	Ridaforolimus 20 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 20 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg intravenously IV on Days 1, 8, 15, & 22 of each 28-day cycle.	
Reporting group title	Ridaforolimus 10 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 10 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg IV on Days 1, 8, 15, & 22 of each 28-day cycle.	

Primary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
End point description:	
PFS is a measure of the time, in months, from randomization to progressive disease or death, whichever occurs earlier.	
End point type	Primary
End point timeframe:	
From randomization to progressive disease or death, whichever occurs first.	

End point values	Ridaforolimus 30 mg + dalotuzumab 10 mg	Exemestane 25 mg	Ridaforolimus 20 mg + dalotuzumab 10 mg	Ridaforolimus 10 mg + dalotuzumab 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	33	27[1]	26[2]
Units: Weeks				
median (confidence interval 95%)	21.4 (15.9 to 43)	24.3 (15.3 to 40.3)	25.7 (16.1 to 31.9)	23.3 (15.6 to 39.3)

Notes:

[1] - No statistical analysis was done for this cohort.

[2] - No statistical analysis was done for this cohort.

Statistical analyses

Statistical analysis title	PFS based on Independent Radiology Review
Statistical analysis description:	
Based on Cox regression model with treatment as a covariate. The model is stratified over proliferation based on Ki67 protein >=15% versus Ki67 protein <15%. One-sided p-value from stratified log-rank test.	
Comparison groups	Ridaforolimus 30 mg + dalotuzumab 10 mg v Exemestane 25

	mg
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	2.19

Secondary: Best overall response

End point title	Best overall response

End point description:

Best overall response indicates the number of participants achieving a complete response (CR), partial response (PR) , or stable disease (SD) at the time of independent radiology review.

End point type	Secondary

End point timeframe:

From randomization to the last evaluation for efficacy (end of therapy visit or discontinuation visit)

End point values	Ridaforolimus 30 mg + dalotuzumab 10 mg	Exemestane 25 mg	Ridaforolimus 20 mg + dalotuzumab 10 mg	Ridaforolimus 10 mg + dalotuzumab 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	33	27	26
Units: Participants				
Complete Response	0	0	0	0
Partial response	1	0	0	0
Stable disease	7	12	12	10

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is presented as the number of participants known to be alive at the time of last data collection (from randomization to date of last data collection for participant, or end of study data collection, whichever came first.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	Ridaforolimus 30 mg + dalotuzumab 10 mg	Exemestane 25 mg	Ridaforolimus 20 mg + dalotuzumab 10 mg	Ridaforolimus 10 mg + dalotuzumab 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	33	27	26
Units: Participants	13	14	17	18

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected for 4 weeks after the last dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Ridaforolimus 30 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 30 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg intravenously (IV) on Days 1, 8, 15, & 22 of each 28-day cycle.	
Reporting group title	Exemestane 25 mg
Reporting group description:	
Participants receive exemestane 25 mg PO once per day.	
Reporting group title	Ridaforolimus 20 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 20 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg IV on Days 1, 8, 15, & 22 of each 28-day cycle.	
Reporting group title	Ridaforolimus 10 mg + dalotuzumab 10 mg
Reporting group description:	
Participants receive ridaforolimus 10 mg PO on Days 1-5, 8-12, 15-19, & 22-26 + dalotuzumab 10 mg/kg IV on Days 1, 8, 15, & 22 of each 28-day cycle.	

Serious adverse events	Ridaforolimus 30 mg + dalotuzumab 10 mg	Exemestane 25 mg	Ridaforolimus 20 mg + dalotuzumab 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 29 (31.03%)	5 / 33 (15.15%)	7 / 27 (25.93%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial neoplasm			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (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
Malignant neoplasm progression			
subjects affected / exposed	1 / 29 (3.45%)	1 / 33 (3.03%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Neoplasm malignant			

subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
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			
Chest pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
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	1 / 29 (3.45%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (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
Pleural effusion			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (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
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	0 / 27 (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
Radius fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	0 / 27 (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
Cardiac disorders			
Myocardial ischaemia			

subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	0 / 27 (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			
Meningism			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	0 / 27 (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 disorders			
Stomatitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			

subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	0 / 27 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	0 / 27 (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
Cellulitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (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
Clostridial infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	0 / 27 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (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
Hyperglycaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	0 / 27 (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	Ridaforolimus 10 mg + dalotuzumab 10 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 26 (26.92%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial neoplasm			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm malignant			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 26 (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	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial ischaemia			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Meningism			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridial infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Sepsis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 26 (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	Ridaforolimus 30 mg + dalotuzumab 10 mg	Exemestane 25 mg	Ridaforolimus 20 mg + dalotuzumab 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)	30 / 33 (90.91%)	27 / 27 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 29 (0.00%)	2 / 33 (6.06%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Hot flush			
subjects affected / exposed	0 / 29 (0.00%)	6 / 33 (18.18%)	0 / 27 (0.00%)
occurrences (all)	0	7	0
Hypertension			
subjects affected / exposed	1 / 29 (3.45%)	1 / 33 (3.03%)	4 / 27 (14.81%)
occurrences (all)	1	1	4
Lymphoedema			

subjects affected / exposed	1 / 29 (3.45%)	2 / 33 (6.06%)	1 / 27 (3.70%)
occurrences (all)	1	2	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 29 (31.03%)	8 / 33 (24.24%)	5 / 27 (18.52%)
occurrences (all)	14	9	5
Chest pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 33 (3.03%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Fatigue			
subjects affected / exposed	11 / 29 (37.93%)	8 / 33 (24.24%)	12 / 27 (44.44%)
occurrences (all)	15	12	17
Oedema			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	3 / 29 (10.34%)	4 / 33 (12.12%)	6 / 27 (22.22%)
occurrences (all)	4	4	9
Pyrexia			
subjects affected / exposed	4 / 29 (13.79%)	2 / 33 (6.06%)	1 / 27 (3.70%)
occurrences (all)	7	3	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Vaginal inflammation			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	12	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 29 (6.90%)	9 / 33 (27.27%)	6 / 27 (22.22%)
occurrences (all)	2	13	6
Dyspnoea			
subjects affected / exposed	1 / 29 (3.45%)	2 / 33 (6.06%)	2 / 27 (7.41%)
occurrences (all)	1	3	3

Epistaxis			
subjects affected / exposed	7 / 29 (24.14%)	2 / 33 (6.06%)	11 / 27 (40.74%)
occurrences (all)	10	2	16
Oropharyngeal pain			
subjects affected / exposed	0 / 29 (0.00%)	5 / 33 (15.15%)	3 / 27 (11.11%)
occurrences (all)	0	5	3
Productive cough			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 33 (3.03%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 29 (17.24%)	2 / 33 (6.06%)	3 / 27 (11.11%)
occurrences (all)	6	2	3
Amylase increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 29 (24.14%)	4 / 33 (12.12%)	2 / 27 (7.41%)
occurrences (all)	7	5	3
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 29 (13.79%)	3 / 33 (9.09%)	1 / 27 (3.70%)
occurrences (all)	4	3	1
Blood bilirubin increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Blood cholesterol increased			
subjects affected / exposed	1 / 29 (3.45%)	1 / 33 (3.03%)	1 / 27 (3.70%)
occurrences (all)	1	2	1
Blood glucose increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	6
Gamma-glutamyltransferase increased			

subjects affected / exposed	6 / 29 (20.69%)	2 / 33 (6.06%)	1 / 27 (3.70%)
occurrences (all)	6	2	1
Haemoglobin decreased			
subjects affected / exposed	3 / 29 (10.34%)	2 / 33 (6.06%)	0 / 27 (0.00%)
occurrences (all)	4	2	0
Lipase increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	3 / 29 (10.34%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences (all)	5	0	2
Weight decreased			
subjects affected / exposed	9 / 29 (31.03%)	0 / 33 (0.00%)	4 / 27 (14.81%)
occurrences (all)	13	0	5
White blood cell count decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Infusion related reaction			
subjects affected / exposed	5 / 29 (17.24%)	0 / 33 (0.00%)	3 / 27 (11.11%)
occurrences (all)	6	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 29 (13.79%)	3 / 33 (9.09%)	0 / 27 (0.00%)
occurrences (all)	5	3	0
Dysgeusia			
subjects affected / exposed	9 / 29 (31.03%)	0 / 33 (0.00%)	9 / 27 (33.33%)
occurrences (all)	12	0	9
Headache			

subjects affected / exposed	5 / 29 (17.24%)	5 / 33 (15.15%)	8 / 27 (29.63%)
occurrences (all)	7	6	14
Hypoaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	2 / 27 (7.41%)
occurrences (all)	0	1	2
Somnolence			
subjects affected / exposed	1 / 29 (3.45%)	1 / 33 (3.03%)	2 / 27 (7.41%)
occurrences (all)	2	3	2
Tremor			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 29 (24.14%)	1 / 33 (3.03%)	7 / 27 (25.93%)
occurrences (all)	9	1	10
Leukopenia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	2
Lymphopenia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 33 (0.00%)	4 / 27 (14.81%)
occurrences (all)	4	0	7
Thrombocytopenia			
subjects affected / exposed	4 / 29 (13.79%)	0 / 33 (0.00%)	4 / 27 (14.81%)
occurrences (all)	7	0	5
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Vertigo			
subjects affected / exposed	2 / 29 (6.90%)	1 / 33 (3.03%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Eye disorders			

Dry eye			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	2
Vision blurred			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 29 (6.90%)	3 / 33 (9.09%)	3 / 27 (11.11%)
occurrences (all)	2	4	3
Abdominal pain upper			
subjects affected / exposed	3 / 29 (10.34%)	4 / 33 (12.12%)	7 / 27 (25.93%)
occurrences (all)	13	4	8
Anal fissure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Constipation			
subjects affected / exposed	5 / 29 (17.24%)	5 / 33 (15.15%)	4 / 27 (14.81%)
occurrences (all)	6	9	4
Diarrhoea			
subjects affected / exposed	14 / 29 (48.28%)	7 / 33 (21.21%)	9 / 27 (33.33%)
occurrences (all)	30	11	28
Dry mouth			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	4 / 27 (14.81%)
occurrences (all)	0	1	4
Dyspepsia			
subjects affected / exposed	1 / 29 (3.45%)	4 / 33 (12.12%)	4 / 27 (14.81%)
occurrences (all)	1	4	6
Dysphagia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 29 (6.90%)	1 / 33 (3.03%)	1 / 27 (3.70%)
occurrences (all)	2	1	1
Haemorrhoids			

subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Nausea			
subjects affected / exposed	13 / 29 (44.83%)	8 / 33 (24.24%)	10 / 27 (37.04%)
occurrences (all)	20	9	15
Proctalgia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Stomatitis			
subjects affected / exposed	26 / 29 (89.66%)	1 / 33 (3.03%)	22 / 27 (81.48%)
occurrences (all)	92	1	47
Vomiting			
subjects affected / exposed	6 / 29 (20.69%)	2 / 33 (6.06%)	6 / 27 (22.22%)
occurrences (all)	18	2	7
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Decubitus ulcer			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Dermatitis acneiform			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	2
Dry skin			
subjects affected / exposed	4 / 29 (13.79%)	1 / 33 (3.03%)	3 / 27 (11.11%)
occurrences (all)	4	1	4
Onychoclasis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Onycholysis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0

Pruritus			
subjects affected / exposed	3 / 29 (10.34%)	2 / 33 (6.06%)	2 / 27 (7.41%)
occurrences (all)	4	2	2
Rash			
subjects affected / exposed	7 / 29 (24.14%)	2 / 33 (6.06%)	7 / 27 (25.93%)
occurrences (all)	9	3	10
Rash maculo-papular			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	4 / 27 (14.81%)
occurrences (all)	2	0	5
Skin lesion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 29 (13.79%)	8 / 33 (24.24%)	4 / 27 (14.81%)
occurrences (all)	4	11	4
Back pain			
subjects affected / exposed	2 / 29 (6.90%)	9 / 33 (27.27%)	3 / 27 (11.11%)
occurrences (all)	2	9	4
Bone pain			
subjects affected / exposed	4 / 29 (13.79%)	1 / 33 (3.03%)	4 / 27 (14.81%)
occurrences (all)	4	1	8
Flank pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Joint stiffness			
subjects affected / exposed	0 / 29 (0.00%)	2 / 33 (6.06%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Muscle spasms			
subjects affected / exposed	5 / 29 (17.24%)	0 / 33 (0.00%)	9 / 27 (33.33%)
occurrences (all)	7	0	10
Muscular weakness			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	5
Musculoskeletal chest pain			

subjects affected / exposed	0 / 29 (0.00%)	3 / 33 (9.09%)	4 / 27 (14.81%)
occurrences (all)	0	4	4
Musculoskeletal pain			
subjects affected / exposed	2 / 29 (6.90%)	4 / 33 (12.12%)	4 / 27 (14.81%)
occurrences (all)	2	4	4
Musculoskeletal stiffness			
subjects affected / exposed	1 / 29 (3.45%)	2 / 33 (6.06%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Myalgia			
subjects affected / exposed	4 / 29 (13.79%)	3 / 33 (9.09%)	3 / 27 (11.11%)
occurrences (all)	4	7	5
Neck pain			
subjects affected / exposed	1 / 29 (3.45%)	4 / 33 (12.12%)	1 / 27 (3.70%)
occurrences (all)	1	4	1
Pain in extremity			
subjects affected / exposed	5 / 29 (17.24%)	5 / 33 (15.15%)	4 / 27 (14.81%)
occurrences (all)	6	5	10
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Influenza			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 29 (3.45%)	2 / 33 (6.06%)	3 / 27 (11.11%)
occurrences (all)	1	3	6
Paronychia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Tooth abscess			
subjects affected / exposed	0 / 29 (0.00%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	4 / 33 (12.12%)	0 / 27 (0.00%)
occurrences (all)	0	6	0

Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)	1 / 33 (3.03%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 29 (44.83%)	7 / 33 (21.21%)	11 / 27 (40.74%)
occurrences (all)	16	8	11
Dehydration			
subjects affected / exposed	4 / 29 (13.79%)	1 / 33 (3.03%)	0 / 27 (0.00%)
occurrences (all)	4	1	0
Hypercholesterolaemia			
subjects affected / exposed	5 / 29 (17.24%)	1 / 33 (3.03%)	1 / 27 (3.70%)
occurrences (all)	6	1	1
Hyperglycaemia			
subjects affected / exposed	11 / 29 (37.93%)	1 / 33 (3.03%)	8 / 27 (29.63%)
occurrences (all)	27	1	10
Hypertriglyceridaemia			
subjects affected / exposed	5 / 29 (17.24%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences (all)	8	0	1
Hypoalbuminaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Hypokalaemia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 33 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	3
Hypomagnesaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Hypophosphataemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 33 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1

Non-serious adverse events	Ridaforolimus 10 mg + dalotuzumab 10 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)		

Vascular disorders			
Flushing			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	9		
Lymphoedema			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 26 (23.08%)		
occurrences (all)	12		
Chest pain			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	13 / 26 (50.00%)		
occurrences (all)	15		
Oedema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		

Vaginal inflammation subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	 6 / 26 (23.08%) 7 3 / 26 (11.54%) 4 5 / 26 (19.23%) 6 1 / 26 (3.85%) 1 2 / 26 (7.69%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 2 / 26 (7.69%) 2		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Amylase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	 3 / 26 (11.54%) 6 3 / 26 (11.54%) 4 4 / 26 (15.38%) 7 1 / 26 (3.85%) 1		

Blood bilirubin increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood cholesterol increased			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Blood glucose increased			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Neutrophil count decreased			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	6		
Platelet count decreased			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	6 / 26 (23.08%)		
occurrences (all)	7		
White blood cell count decreased			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Infusion related reaction			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	8 / 26 (30.77%)		
occurrences (all)	11		
Headache			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	5		
Hypoaesthesia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	7		
Leukopenia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	6		
Thrombocytopenia			

subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	5		
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Anal fissure			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	13 / 26 (50.00%)		
occurrences (all)	21		
Dry mouth			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Dyspepsia			

subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	9 / 26 (34.62%)		
occurrences (all)	11		
Proctalgia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	22 / 26 (84.62%)		
occurrences (all)	52		
Vomiting			
subjects affected / exposed	8 / 26 (30.77%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Decubitus ulcer			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Dermatitis acneiform			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		

Dry skin subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2		
Onychoclasis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Onycholysis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 4		
Rash subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 5		
Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Skin lesion subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 5		
Back pain subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 5		
Bone pain subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 4		
Flank pain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Joint stiffness			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	9		
Muscular weakness			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	6 / 26 (23.08%)		
occurrences (all)	9		
Neck pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		

Paronychia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	6		
Dehydration			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	8		
Hypertriglyceridaemia			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		
Hypoalbuminaemia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Hypomagnesaemia			

subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		
Hypophosphataemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2011	Amendment 2 was done to inform investigators of a tolerability run-in and to provide Investigators with more consistent guidelines and encourage aggressive treatment of stomatitis before it reached a toxicity Grade of 3.
28 June 2012	Amendment 3 was done to cancel the planned Part B of this study that was designed to compare the combination regimens to each of the single agents in the combination.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 May 2011	Enrollment was interrupted while the protocol was amended to lower the dose due to combination toxicity.	26 August 2011

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Because Part B of the study was cancelled, no inferential testing was performed and p-values are for descriptive purposes only.

Notes: