Clinical trial results:
A Phase Ib/II Randomized Study of BI 836845 in Combination with Exemestane and Everolimus Versus Exemestane and Everolimus Alone in Women with Locally Advanced or Metastatic Breast Cancer

Summary

EudraCT number	2013-001110-15
Trial protocol	ES FR BE NL SE IE AT
Global end of trial date	14 December 2021

Results information

Result version number	v1 (current)
This version publication date	25 December 2022
First version publication date	25 December 2022

Trial information

Trial identification

Sponsor protocol code	1280.4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02123823
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.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	24 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 November 2016
Global end of trial reached?	Yes
Global end of trial date	14 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of this trial was to determine the Maximum Tolerated Dose and Recommended Phase II Dose, and to evaluate the safety and antitumour activity, of BI 836845 and everolimus in combination with exemestane in women with HR+/HER2- advanced breast cancer.

Protection of trial subjects:

All patients were free to withdraw their consent at any time during the study without penalty or prejudice. Their personal trialrelated data would be considered confidential and used by BI in accordance with the local data protection laws. The level of disclosure was explained to the patients. Their medical records could be examined by Clinical Quality Assurance auditors appointed by BI, by members of the appropriate IEC/IRB, and by inspectors from regulatory authorities. Confidentiality of patient data was ensured by the use of depersonalised patient identification codes (patient numbers). The terms and conditions of the insurance cover were available to the investigator and the patients in the Investigator Site File (ISF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 May 2014
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	Belgium: 31
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 66
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Ireland: 13
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 21
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	United Kingdom: 15
Worldwide total number of subjects	202
EEA total number of subjects	156

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)	124
From 65 to 84 years	77
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This is a phase Ib/II, randomized, open label study to determine the maximum tolerated dose (MTD) and the recommended phase II dose and to evaluate the anti-tumor activity of BI 836845 (xentuzumab) in combination with exemestane and everolimus versus exemestane and everolimus alone in women with locally advanced or metastatic breast cancer.

Pre-assignment

Screening details:

Subjects that met eligibility criteria entered. Subjects could withdraw at any time/reason. If subject continued take drug, close monitoring was adhered to+adverse events recorded. Rules implemented in all trials whereby doses be reduced if required. If further events reported, withdrawn. Symptomatic treatment of tumour associated symptoms allowed.

Period 1

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

Blinding implementation details:

Open label

Arms

Are arms mutually exclusive?	Yes
Arm title	xentuzumab 750mg+everolimus 10mg+exemestane 25mg - Phase Ib

Arm description:

Subjects received a single dose of 750 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Arm type	Experimental
Investigational medicinal product name	xentuzumab (BI 836845)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single dose of 750 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal.

Investigational medicinal product name	exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose once daily (qd) of 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Investigational medicinal product name	everolimus
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Arm title	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase Ib

Arm description:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Arm type	Experimental
Investigational medicinal product name	xentuzumab (BI 836845)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal.

Investigational medicinal product name	exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose once daily (qd) of 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Investigational medicinal product name	everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Arm title	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II

Arm description:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting on Day 1 continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Administration of xentuzumab was stopped after 28th October 2016, and participants in this group who remained in the trial could continue with everolimus 10 mg + exemestane 25 mg.

Arm type	Experimental

Investigational medicinal product name	xentuzumab (BI 836845)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal.

Investigational medicinal product name	everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Investigational medicinal product name	exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose once daily (qd) of 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Arm title	everolimus 10 mg + exemestane 25 mg - Phase II

Arm description:

Subjects received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting on Day 1 continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

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

Dosage and administration details:

Subjects received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Investigational medicinal product name	exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose once daily (qd) of 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Number of subjects in period 1[1]	xentuzumab 750mg+everolimus 10mg+exemestane 25mg - Phase Ib	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase Ib	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II
Started	3	21	70
Treated	3	21	70
Completed	0	0	0
Not completed	3	21	70
Consent withdrawn by subject	-	-	7
Adverse event, non-fatal	-	-	3
Progressive disease	3	19	52
Lack of efficacy	-	2	8

Number of subjects in period 1[1]	everolimus 10 mg + exemestane 25 mg - Phase II
Started	70
Treated	69
Completed	0
Not completed	70
Consent withdrawn by subject	2
Adverse event, non-fatal	5
Progressive disease	53
Lack of efficacy	10

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 202 subjects who were enrolled in the trial, only 164 were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	xentuzumab 750mg+everolimus 10mg+exemestane 25mg - Phase Ib

Reporting group description:

Subjects received a single dose of 750 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Reporting group title	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase Ib

Reporting group description:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Reporting group title	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II

Reporting group description:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting on Day 1 continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Administration of xentuzumab was stopped after 28th October 2016, and participants in this group who remained in the trial could continue with everolimus 10 mg + exemestane 25 mg.

Reporting group title	everolimus 10 mg + exemestane 25 mg - Phase II

Reporting group description:

Subjects received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting on Day 1 continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Reporting group values	xentuzumab 750mg+everolimus 10mg+exemestane 25mg - Phase Ib	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase Ib	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II
Number of subjects	3	21	70
Age categorical			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0

Adults (18-64 years)	2	9	47
From 65-84 years	1	12	22
85 years and over	0	0	1

Age Continuous			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: years			
arithmetic mean	59.00	64.33	60.17
standard deviation	± 8.00	± 7.84	± 9.61

Sex: Female, Male			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: Participants			
Female	3	21	70
Male	0	0	0

Race (NIH/OMB)			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	21	53
More than one race	0	0	0
Unknown or Not Reported	0	0	5

Ethnicity (NIH/OMB)			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: Subjects			
Hispanic or Latino	0	2	1
Not Hispanic or Latino	3	19	62
Unknown or Not Reported	0	0	7

Reporting group values	everolimus 10 mg + exemestane 25 mg - Phase II	Total	
Number of subjects	70	164	
Age categorical			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1).			

Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	44	102	
From 65-84 years	26	61	
85 years and over	0	1	
Age Continuous			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: years			
arithmetic mean	60.67		
standard deviation	± 9.07	-	
Sex: Female, Male			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: Participants			
Female	70	164	
Male	0	0	
Race (NIH/OMB)			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	12	24	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	51	128	
More than one race	0	0	
Unknown or Not Reported	7	12	
Ethnicity (NIH/OMB)			
Treated set (Phase Ib only): This patient set included all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1). Randomised set (RS) (Phase II only): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.			
Units: Subjects			

Hispanic or Latino	5	8	
Not Hispanic or Latino	57	141	
Unknown or Not Reported	8	15	

End points

End points reporting groups

Reporting group title	xentuzumab 750mg+everolimus 10mg+exemestane 25mg - Phase Ib

Reporting group description:

Subjects received a single dose of 750 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Reporting group title	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase Ib

Reporting group description:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Reporting group title	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II

Reporting group description:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting on Day 1 continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Administration of xentuzumab was stopped after 28th October 2016, and participants in this group who remained in the trial could continue with everolimus 10 mg + exemestane 25 mg.

Reporting group title	everolimus 10 mg + exemestane 25 mg - Phase II

Reporting group description:

Subjects received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting on Day 1 continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Subject analysis set title	xentuzumab (BI 836845)
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment group "xentuzumab (BI 836845) comprises all dose cohorts during the dose finding phase, that is, "xentuzumab (BI 836845) 750 mg + everolimus 10 mg + exemestane 25 mg" and "xentuzumab (BI 836845) 1000 mg + everolimus 10 mg + exemestane 25 mg".
All patients were administered doses of xentuzumab (BI 836845) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course in the absence of disease progression, intolerable AEs or other reason necessitating withdrawal.
Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting 7 days before first administration of BI 836845 (xentuzumab) continously in the absence of disease progression, intolerable AEs or other reason necessitating withdrawal.

Primary: Progression-free survival (PFS) - Phase II part

End point title	Progression-free survival (PFS) - Phase II part[1]

End point description:

Progression-free survival (PFS) in the phase II part is presented.
PFS was defined as the time from randomisation until radiological tumour progression according to RECIST 1.1, or death from any cause, whichever occurred earlier. Clinical disease progression was not considered for determination of a PFS event, unless the outcome of the progression was death. The cut-off date was 25th November 2016. At cut-off date, xentuzumab was discontinued in all patients in the experimental arm per sponsor decision, recruitment was also terminated. Patients who discontinued xentuzumab treatment continued with everolimus 10 mg + exemestane 25 mg treatment.

99999 = not available (not calculable)

Randomised set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab (BI 836845) in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.

End point type	Primary

End point timeframe:

From randomisation until radiological tumour progression according to RECIST 1.1, or death from any cause or data cut-off (25Nov2016), up to 32.2 months.

Notes:

[1] - 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: This endpoint only reports results for phase II of the study, therefore arms belonging to phase Ib are not reported here.

End point values	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II	everolimus 10 mg + exemestane 25 mg - Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	70		
Units: Months				
median (confidence interval 95%)	7.3 (3.3 to 99999)	5.6 (3.7 to 9.1)		

Statistical analyses

Statistical analysis title	Log Rank analysis
Comparison groups	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II v everolimus 10 mg + exemestane 25 mg - Phase II
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9057
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.65

Primary: Number of patients with dose limiting toxicity (DLT) - phase Ib part

End point title	Number of patients with dose limiting toxicity (DLT) - phase Ib part[2][3]

End point description:

Number of patients with dose limiting toxicity (DLT) in phase Ib part is presented.

Treated set (Phase Ib only): This patient set included all patients who were documented to have

received and taken at least one dose of any study medication during the treatment cycles (from Day 1).

End point type	Primary

End point timeframe:

From first administration of study treatment until end of first treatment cycle, up to 28 days.

Notes:

[2] - 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: The primary endpoint was only analysed descriptively.

[3] - 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: This endpoint only reports results for phase II of the study, therefore arms belonging to phase Ib are not reported here.

End point values	xentuzumab 750mg+everolimus 10mg+exemestane 25mg - Phase Ib	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase Ib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Tolerated Dose (MTD) - phase Ib part

End point title	Maximum Tolerated Dose (MTD) - phase Ib part[4]

End point description:

The Maximum Tolerated Dose (MTD) in this study was defined as the highest dose level examined of trial medication, at which no more than 1 out of 6 patients experienced a DLT during the MTD evaluation period.

Maximum tolerated dose (MTD) set: The MTD set defined the set of patients in the Phase Ib part who were fully evaluable for determination of the MTD in the first treatment course. The MTD set was used for some safety analyses in the escalation part.
The MTD evaluation period was defined as the time from the first administration of xentuzumab up to start of cycle 2.
A "3+3" Phase Ib dose finding phase was performed to determine the MTD.

End point type	Primary

End point timeframe:

up to 28 days.

Notes:

[4] - 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: The primary endpoint was only analysed descriptively.

End point values	xentuzumab (BI 836845)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: milligrams (mg)	1000			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with objective response (OR) - phase II part

End point title	Number of patients with objective response (OR) - phase II part[5]

End point description:

Objective response (OR) - phase II part is presented.
Objective response (OR), defined as best overall response of complete response (CR) or partial response (PR), where best overall response was determined according to RECIST 1.1 from date of randomisation until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

Randomised set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab (BI 836845) in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.

End point type	Secondary

End point timeframe:

From randomisation until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy or data cut-off (25Nov2016), up to 32.2 months.

Notes:

[5] - 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: This endpoint only reports results for phase II of the study, therefore arms belonging to phase Ib are not reported here.

End point values	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II	everolimus 10 mg + exemestane 25 mg - Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	70		
Units: Participants	5	7		

Statistical analyses

Statistical analysis title	Logistic regression analysis
Comparison groups	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II v everolimus 10 mg + exemestane 25 mg - Phase II

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5598
Method	Regression, Logistic
Parameter estimate	Log odds ratio
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.32

Secondary: Time to progression (TTP) - phase II part

End point title	Time to progression (TTP) - phase II part[6]

End point description:

Time to progression (TTP) is presented.
Time to progression (TTP), defined as the time from the date of randomization until the date of the first objective tumour progression according to RECIST 1.1.
99999 = not available (not calculable)

Randomised set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab (BI 836845) in combination with exemestane and everolimus or exemestane and everolimus alone as randomised. Only patients with progression were analysed.

End point type	Secondary

End point timeframe:

From randomisation until the date of the first objective tumour progression according to RECIST 1.1. or data cut-off (25Nov2016), up to 32.2 months.

Notes:

[6] - 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: This endpoint only reports results for phase II of the study, therefore arms belonging to phase Ib are not reported here.

End point values	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II	everolimus 10 mg + exemestane 25 mg - Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	70		
Units: Months				
median (confidence interval 95%)	7.3 (3.7 to 99999)	5.6 (5.3 to 9.1)		

Statistical analyses

Statistical analysis title	Log Rank analysis
Comparison groups	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II v everolimus 10 mg + exemestane 25 mg - Phase II

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9146
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.8

Secondary: Number of patients with disease control (DC) - phase II part

End point title	Number of patients with disease control (DC) - phase II part[7]

End point description:

Disease control is defined as best overall response of complete response (CR) or partial response (PR), or stable disease (SD) >= 24 weeks, or Non−CR/Non−PD for >= 24 weeks. PD=Progressive disease.

Randomised set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab (BI 836845) in combination with exemestane and everolimus or exemestane and everolimus alone as randomised.

End point type	Secondary

End point timeframe:

From randomisation until data cut-off (25Nov2016), up to 32.2 months.

Notes:

[7] - 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: This endpoint only reports results for phase II of the study, therefore arms belonging to phase Ib are not reported here.

End point values	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II	everolimus 10 mg + exemestane 25 mg - Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	70		
Units: Participants	13	17		

Statistical analyses

Statistical analysis title	Logistic regression analysis
Comparison groups	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II v everolimus 10 mg + exemestane 25 mg - Phase II

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4008
Method	Regression, Logistic
Parameter estimate	Log odds ratio
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.59

Secondary: Time to objective response - phase II part

End point title	Time to objective response - phase II part[8]

End point description:

Time to objective response is presented.
Time to objective response is defined as the time from randomisation until first documented complete response (CR) or partial response (PR).

Randomised set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab (BI 836845) in combination with exemestane and everolimus or exemestane and everolimus alone as randomised. Only patients with objective response were analysed.

End point type	Secondary

End point timeframe:

From randomisation until first documented complete response (CR) or partial response (PR) or data cut-off (25Nov2016), up to 32.2 months.

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: This endpoint only reports results for phase II of the study, therefore arms belonging to phase Ib are not reported here.

End point values	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II	everolimus 10 mg + exemestane 25 mg - Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: Months				
median (inter-quartile range (Q1-Q3))	3.7 (3.6 to 5.3)	1.8 (1.7 to 5.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response - phase II part

End point title	Duration of objective response - phase II part[9]

End point description:

Duration of objective response is presented.
Duration of objective response is defined as the time from first documented complete response (CR) or partial response (PR) until the earliest of disease progression or death among patients with objective response (OR).
99999 = not available (not calculable)

Randomised set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab (BI 836845) in combination with exemestane and everolimus or exemestane and everolimus alone as randomised. Only patients with objective response were analysed.

End point type	Secondary

End point timeframe:

From randomisation until the earliest of disease progression or death or data cut-off (25Nov2016), up to 32.2 months.

Notes:

[9] - 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: This endpoint only reports results for phase II of the study, therefore arms belonging to phase Ib are not reported here.

End point values	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II	everolimus 10 mg + exemestane 25 mg - Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: Months				
median (inter-quartile range (Q1-Q3))	5.6 (5.6 to 5.6)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control - phase II part

End point title	Duration of disease control - phase II part[10]

End point description:

Duration of disease control is presented.
Duration of disease control is defined as the time from randomisation until the earliest of disease progression or death, among patients with disease control.
99999 = not available (not calculable)

Randomised set (RS): This patient set included all randomised patients in the Phase II part, regardless of whether or not they received treatment. Patients were assigned to xentuzumab (BI 836845) in combination with exemestane and everolimus or exemestane and everolimus alone as randomised. Only patients with disease control were analysed.

End point type	Secondary

End point timeframe:

From randomisation until the earliest of disease progression or death or data cut-off (25Nov2016), up to 32.2 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: This endpoint only reports results for phase II of the study, therefore arms belonging to

phase Ib are not reported here.

End point values	xentuzumab 1000mg+everolimus 10mg+exemestane 25mg - Phase II	everolimus 10 mg + exemestane 25 mg - Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: Months				
median (inter-quartile range (Q1-Q3))	99999 (10.9 to 99999)	9.3 (9.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Phase Ib: from first dose until last dose + 42 days of residual effect period, up to 54.3 months + 42 days Phase II: from first dose until last dose + 42 days of residual effect period, up to 37.7 months + 42 days

Adverse event reporting additional description:

Treated set (Ib): all patients who were documented to have received and taken at least one dose of any study medication during the treatment cycles (from Day 1).
Randomised set (II): all randomised patients, regardless of whether or not they received treatment.
AEs were reported by initial treatment as planned in the Statistical Analysis Plan.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Xentuzumab 750mg + Ev 10mg + Ex 25mg - Phase Ib

Reporting group description:

Subjects received a single dose of 750 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus (Ev) and 1 tablet of 25 mg exemestane (Ex) starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Reporting group title	Xentuzumab 1000 mg + Ev 10 mg + Ex 25 mg - Phase Ib

Reporting group description:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable adverse events (AEs) or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus (Ev) and 1 tablet of 25 mg exemestane (Ex) starting 7 days before first administration of BI 836845 (xentuzumab) continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Reporting group title	Xentuzumab 1000 mg + Ev 10 mg + Ex 25 mg - Phase II

Reporting group description:

Subjects received a single dose of 1000 milligram (mg) BI 836845 (xentuzumab) as a 1 hour (h) intravenous infusion once a week on Day 1, 8, 15 and 22 in a 28-day course until disease progression, intolerable AEs or other reason necessitating withdrawal. Subjects also received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting on Day 1 continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Administration of xentuzumab was stopped after 28th October 2016, and participants in this group who remained in the trial could continue with everolimus 10 mg + exemestane 25 mg.

Reporting group title	everolimus 10 mg + exemestane 25 mg - Phase II

Reporting group description:

Subjects received a single oral dose once daily (qd) of 2x 5 mg (10 mg total) tablets of everolimus and 1 tablet of 25 mg exemestane starting on Day 1 continously until disease progression, intolerable AEs or other reason necessitating withdrawal.

Serious adverse events	Xentuzumab 750mg + Ev 10mg + Ex 25mg - Phase Ib	Xentuzumab 1000 mg + Ev 10 mg + Ex 25 mg - Phase Ib	Xentuzumab 1000 mg + Ev 10 mg + Ex 25 mg - Phase II
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	10 / 21 (47.62%)	20 / 70 (28.57%)
number of deaths (all causes)	0	2	9
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burkitt's lymphoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	3 / 3 (100.00%)	5 / 21 (23.81%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to peritoneum			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Sarcoma uterus			

subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Peripheral venous disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Feeling cold			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (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
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Interstitial lung disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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

Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumothorax			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Reexpansion pulmonary oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pelvic fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Pericardial effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Febrile neutropenia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 70 (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
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (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
Vertigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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			
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Ascites			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (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
Subileus			

subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (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
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Renal failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
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			
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteonecrosis of jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (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 / 3 (0.00%)	0 / 21 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (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
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Scrub typhus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Soft tissue infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (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
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	0 / 70 (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
Hypophosphataemia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (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

Serious adverse events	everolimus 10 mg + exemestane 25 mg - Phase II		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 69 (42.03%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Burkitt's lymphoma			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 69 (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 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to peritoneum			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Sarcoma uterus			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Lymphoedema			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral venous disease			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subclavian vein thrombosis			
subjects affected / exposed	0 / 69 (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	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Feeling cold				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Pleural effusion				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	5 / 69 (7.25%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Reexpansion pulmonary oedema				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Neutrophil count decreased				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Brain contusion				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pelvic fracture			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 69 (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	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Deafness				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertigo				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain upper				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				

subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Renal failure			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Osteonecrosis of jaw				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Scrub typhus				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				

subjects affected / exposed	0 / 69 (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	Xentuzumab 750mg + Ev 10mg + Ex 25mg - Phase Ib	Xentuzumab 1000 mg + Ev 10 mg + Ex 25 mg - Phase Ib	Xentuzumab 1000 mg + Ev 10 mg + Ex 25 mg - Phase II
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	21 / 21 (100.00%)	70 / 70 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	4 / 70 (5.71%)
occurrences (all)	0	3	5
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	9 / 21 (42.86%)	8 / 70 (11.43%)
occurrences (all)	0	36	14
Lymphoedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	7 / 70 (10.00%)
occurrences (all)	0	1	10
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 3 (100.00%)	9 / 21 (42.86%)	23 / 70 (32.86%)
occurrences (all)	8	35	56
Calcinosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	5 / 70 (7.14%)
occurrences (all)	0	0	5
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	9 / 21 (42.86%)	19 / 70 (27.14%)
occurrences (all)	0	19	26
Influenza like illness			

subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	1
Mucosal dryness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	2 / 70 (2.86%)
occurrences (all)	0	3	2
Mucosal inflammation			
subjects affected / exposed	3 / 3 (100.00%)	10 / 21 (47.62%)	27 / 70 (38.57%)
occurrences (all)	5	33	61
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	5 / 21 (23.81%)	11 / 70 (15.71%)
occurrences (all)	2	6	18
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	7 / 21 (33.33%)	10 / 70 (14.29%)
occurrences (all)	1	9	12
Reproductive system and breast disorders			
Vulvovaginal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	4 / 70 (5.71%)
occurrences (all)	0	0	6
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	2 / 70 (2.86%)
occurrences (all)	1	0	2
Cough			
subjects affected / exposed	1 / 3 (33.33%)	10 / 21 (47.62%)	25 / 70 (35.71%)
occurrences (all)	1	18	34
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	6 / 21 (28.57%)	12 / 70 (17.14%)
occurrences (all)	1	9	15
Dyspnoea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	4 / 70 (5.71%)
occurrences (all)	0	0	6
Epistaxis			

subjects affected / exposed	0 / 3 (0.00%)	9 / 21 (42.86%)	13 / 70 (18.57%)
occurrences (all)	0	11	16
Interstitial lung disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 70 (0.00%)
occurrences (all)	0	2	0
Nasal dryness			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	0 / 70 (0.00%)
occurrences (all)	0	3	0
Pneumonitis			
subjects affected / exposed	1 / 3 (33.33%)	9 / 21 (42.86%)	7 / 70 (10.00%)
occurrences (all)	3	22	10
Productive cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	5 / 70 (7.14%)
occurrences (all)	0	1	9
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	8 / 70 (11.43%)
occurrences (all)	0	4	8
Sleep disorder			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	0	2	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	5 / 21 (23.81%)	18 / 70 (25.71%)
occurrences (all)	1	20	29
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	4 / 21 (19.05%)	14 / 70 (20.00%)
occurrences (all)	1	9	23
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	1	4	1
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 3 (66.67%)	7 / 21 (33.33%)	11 / 70 (15.71%)
occurrences (all)	8	24	22
Blood cholesterol increased			

subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	1 / 70 (1.43%)
occurrences (all)	0	3	1
Blood creatinine increased			
subjects affected / exposed	1 / 3 (33.33%)	5 / 21 (23.81%)	3 / 70 (4.29%)
occurrences (all)	2	13	3
Blood glucose increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	0	2	1
Blood iron decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	0	4	5
Blood phosphorus decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	3 / 70 (4.29%)
occurrences (all)	0	4	4
Blood triglycerides increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 21 (9.52%)	5 / 70 (7.14%)
occurrences (all)	2	13	6
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	4 / 21 (19.05%)	2 / 70 (2.86%)
occurrences (all)	0	12	12
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	5 / 21 (23.81%)	8 / 70 (11.43%)
occurrences (all)	0	13	12
Low density lipoprotein increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	3 / 70 (4.29%)
occurrences (all)	0	7	5
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	4 / 21 (19.05%)	8 / 70 (11.43%)
occurrences (all)	1	14	20
Platelet count decreased			
subjects affected / exposed	2 / 3 (66.67%)	4 / 21 (19.05%)	14 / 70 (20.00%)
occurrences (all)	9	5	23
Weight decreased			
subjects affected / exposed	1 / 3 (33.33%)	11 / 21 (52.38%)	6 / 70 (8.57%)
occurrences (all)	1	25	9

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	0	2	1
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	2 / 70 (2.86%)
occurrences (all)	0	3	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	4 / 70 (5.71%)
occurrences (all)	0	2	4
Dysgeusia			
subjects affected / exposed	1 / 3 (33.33%)	8 / 21 (38.10%)	10 / 70 (14.29%)
occurrences (all)	1	8	14
Headache			
subjects affected / exposed	0 / 3 (0.00%)	5 / 21 (23.81%)	17 / 70 (24.29%)
occurrences (all)	0	7	26
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 3 (100.00%)	13 / 21 (61.90%)	16 / 70 (22.86%)
occurrences (all)	11	48	48
Iron deficiency anaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	0	11	2
Leukopenia			
subjects affected / exposed	1 / 3 (33.33%)	6 / 21 (28.57%)	7 / 70 (10.00%)
occurrences (all)	1	23	7
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	6 / 70 (8.57%)
occurrences (all)	0	24	7
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	8 / 21 (38.10%)	20 / 70 (28.57%)
occurrences (all)	4	26	57
Thrombocytopenia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 21 (19.05%)	17 / 70 (24.29%)
occurrences (all)	1	14	40

Eye disorders			
Visual acuity reduced			
subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Xerophthalmia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	4 / 21 (19.05%)	11 / 70 (15.71%)
occurrences (all)	1	12	12
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	5 / 21 (23.81%)	6 / 70 (8.57%)
occurrences (all)	2	5	9
Aphthous ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 70 (1.43%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	3 / 21 (14.29%)	15 / 70 (21.43%)
occurrences (all)	2	3	29
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	12 / 21 (57.14%)	31 / 70 (44.29%)
occurrences (all)	0	53	73
Dry mouth			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	3 / 70 (4.29%)
occurrences (all)	0	2	3
Dyspepsia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 21 (9.52%)	5 / 70 (7.14%)
occurrences (all)	1	3	5
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	3 / 70 (4.29%)
occurrences (all)	0	3	3
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	3 / 70 (4.29%)
occurrences (all)	0	6	4
Nausea			

subjects affected / exposed	1 / 3 (33.33%)	9 / 21 (42.86%)	24 / 70 (34.29%)
occurrences (all)	3	23	40
Odynophagia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 21 (4.76%)	3 / 70 (4.29%)
occurrences (all)	1	1	3
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	8 / 21 (38.10%)	24 / 70 (34.29%)
occurrences (all)	0	24	67
Tooth loss			
subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	0 / 70 (0.00%)
occurrences (all)	0	3	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	7 / 21 (33.33%)	14 / 70 (20.00%)
occurrences (all)	3	18	22
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 21 (9.52%)	3 / 70 (4.29%)
occurrences (all)	1	2	3
Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	0	4	1
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	8 / 70 (11.43%)
occurrences (all)	0	4	9
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	3 / 70 (4.29%)
occurrences (all)	0	3	3
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 21 (0.00%)	5 / 70 (7.14%)
occurrences (all)	0	0	6
Nail disorder			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	5 / 70 (7.14%)
occurrences (all)	0	2	7

Nail dystrophy			
subjects affected / exposed	0 / 3 (0.00%)	5 / 21 (23.81%)	2 / 70 (2.86%)
occurrences (all)	0	7	2
Onychoclasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	3 / 70 (4.29%)
occurrences (all)	0	1	3
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	6 / 21 (28.57%)	14 / 70 (20.00%)
occurrences (all)	0	10	15
Rash			
subjects affected / exposed	2 / 3 (66.67%)	6 / 21 (28.57%)	25 / 70 (35.71%)
occurrences (all)	4	9	42
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	3 / 70 (4.29%)
occurrences (all)	0	1	4
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	2 / 70 (2.86%)
occurrences (all)	0	2	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	4 / 21 (19.05%)	1 / 70 (1.43%)
occurrences (all)	0	9	1
Urinary incontinence			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	0 / 70 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 21 (19.05%)	11 / 70 (15.71%)
occurrences (all)	1	7	22
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	6 / 21 (28.57%)	12 / 70 (17.14%)
occurrences (all)	0	6	16
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	5 / 70 (7.14%)
occurrences (all)	0	3	6
Muscle spasms			

subjects affected / exposed	1 / 3 (33.33%)	4 / 21 (19.05%)	8 / 70 (11.43%)
occurrences (all)	2	5	8
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	4 / 21 (19.05%)	8 / 70 (11.43%)
occurrences (all)	0	5	12
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	6 / 70 (8.57%)
occurrences (all)	0	3	6
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	8 / 70 (11.43%)
occurrences (all)	0	3	11
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	2 / 70 (2.86%)
occurrences (all)	0	2	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	4 / 70 (5.71%)
occurrences (all)	0	1	7
Cystitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	4 / 70 (5.71%)
occurrences (all)	0	2	5
Diverticulitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	2 / 70 (2.86%)
occurrences (all)	0	4	3
Gingivitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	3 / 70 (4.29%)
occurrences (all)	0	2	3
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	5 / 21 (23.81%)	12 / 70 (17.14%)
occurrences (all)	0	12	18
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	1 / 21 (4.76%)	2 / 70 (2.86%)
occurrences (all)	0	1	2

Paronychia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 70 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 3 (33.33%)	2 / 21 (9.52%)	2 / 70 (2.86%)
occurrences (all)	2	2	3
Tooth abscess			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	2 / 70 (2.86%)
occurrences (all)	0	2	3
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	5 / 70 (7.14%)
occurrences (all)	0	6	6
Tooth infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	0	2	1
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	6 / 21 (28.57%)	7 / 70 (10.00%)
occurrences (all)	0	6	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	13 / 21 (61.90%)	18 / 70 (25.71%)
occurrences (all)	1	28	25
Hypercholesterolaemia			
subjects affected / exposed	1 / 3 (33.33%)	5 / 21 (23.81%)	7 / 70 (10.00%)
occurrences (all)	4	36	16
Hyperglycaemia			
subjects affected / exposed	3 / 3 (100.00%)	11 / 21 (52.38%)	18 / 70 (25.71%)
occurrences (all)	8	44	41
Hypertriglyceridaemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 21 (14.29%)	5 / 70 (7.14%)
occurrences (all)	0	12	8
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 21 (19.05%)	4 / 70 (5.71%)
occurrences (all)	0	6	7
Hypocalcaemia			

subjects affected / exposed	1 / 3 (33.33%)	4 / 21 (19.05%)	7 / 70 (10.00%)
occurrences (all)	3	9	12
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 70 (1.43%)
occurrences (all)	0	2	1
Hypophosphataemia			
subjects affected / exposed	1 / 3 (33.33%)	7 / 21 (33.33%)	11 / 70 (15.71%)
occurrences (all)	1	26	34

Non-serious adverse events	everolimus 10 mg + exemestane 25 mg - Phase II		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 69 (98.55%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	15		
Lymphoedema			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	5		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 69 (34.78%)		
occurrences (all)	49		
Calcinosis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	17 / 69 (24.64%)		
occurrences (all)	25		
Influenza like illness			

subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 5		
Mucosal dryness subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1		
Mucosal inflammation subjects affected / exposed occurrences (all)	22 / 69 (31.88%) 46		
Oedema peripheral subjects affected / exposed occurrences (all)	16 / 69 (23.19%) 21		
Pyrexia subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 8		
Reproductive system and breast disorders Vulvovaginal inflammation subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Aphonia subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Dysphonia subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2		
Cough subjects affected / exposed occurrences (all)	18 / 69 (26.09%) 36		
Dyspnoea subjects affected / exposed occurrences (all)	18 / 69 (26.09%) 28		
Dyspnoea exertional subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 5		
Epistaxis			

subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	15		
Interstitial lung disease			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Nasal dryness			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Pneumonitis			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	11		
Productive cough			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	8		
Sleep disorder			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 69 (15.94%)		
occurrences (all)	24		
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 69 (20.29%)		
occurrences (all)	25		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	4		
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	19		
Blood cholesterol increased			

subjects affected / exposed	6 / 69 (8.70%)			
occurrences (all)	13			
Blood creatinine increased				
subjects affected / exposed	4 / 69 (5.80%)			
occurrences (all)	5			
Blood glucose increased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences (all)	1			
Blood iron decreased				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences (all)	3			
Blood phosphorus decreased				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences (all)	2			
Blood triglycerides increased				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences (all)	2			
Haemoglobin decreased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences (all)	1			
Gamma-glutamyltransferase increased				
subjects affected / exposed	7 / 69 (10.14%)			
occurrences (all)	18			
Low density lipoprotein increased				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences (all)	2			
Neutrophil count decreased				
subjects affected / exposed	2 / 69 (2.90%)			
occurrences (all)	4			
Platelet count decreased				
subjects affected / exposed	3 / 69 (4.35%)			
occurrences (all)	6			
Weight decreased				
subjects affected / exposed	9 / 69 (13.04%)			
occurrences (all)	17			

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	6		
Dysgeusia			
subjects affected / exposed	9 / 69 (13.04%)		
occurrences (all)	10		
Headache			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	15		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 69 (23.19%)		
occurrences (all)	35		
Iron deficiency anaemia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	19		
Lymphopenia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	33		
Neutropenia			
subjects affected / exposed	11 / 69 (15.94%)		
occurrences (all)	29		
Thrombocytopenia			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	37		

Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Xerophthalmia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	7		
Abdominal pain upper			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	7		
Aphthous ulcer			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	23 / 69 (33.33%)		
occurrences (all)	39		
Dry mouth			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	4		
Mouth ulceration			
subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	17		
Nausea			

subjects affected / exposed occurrences (all)	16 / 69 (23.19%) 24		
Odynophagia subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2		
Stomatitis subjects affected / exposed occurrences (all)	26 / 69 (37.68%) 53		
Tooth loss subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Toothache subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 3		
Vomiting subjects affected / exposed occurrences (all)	15 / 69 (21.74%) 20		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Dermatitis subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Dry skin subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 8		
Eczema subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Erythema subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 6		
Nail disorder subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1		

Nail dystrophy subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Onychoclasis subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Pruritus subjects affected / exposed occurrences (all)	15 / 69 (21.74%) 16		
Rash subjects affected / exposed occurrences (all)	23 / 69 (33.33%) 50		
Rash maculo-papular subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5		
Urticaria subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 3		
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	17 / 69 (24.64%) 27		
Back pain subjects affected / exposed occurrences (all)	13 / 69 (18.84%) 17		
Bone pain subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5		
Muscle spasms			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	7		
Myalgia			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	8		
Pain in jaw			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	5		
Cystitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Diverticulitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	2		
Gingivitis			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	14		
Oral herpes			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		

Paronychia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Tooth abscess			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	15		
Tooth infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	9 / 69 (13.04%)		
occurrences (all)	11		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 69 (31.88%)		
occurrences (all)	35		
Hypercholesterolaemia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	9		
Hyperglycaemia			
subjects affected / exposed	17 / 69 (24.64%)		
occurrences (all)	36		
Hypertriglyceridaemia			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	12		
Hypokalaemia			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	7		
Hypocalcaemia			

subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	6		
Hypomagnesaemia			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	8 / 69 (11.59%)		
occurrences (all)	16		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2015	Several clarifications for accuracy, corrections, and terminology updates were made. The criteria for safety was updated adding the determination of MTD (synopsis). It was clarified that PK sampling should be taken before and at the end of xentuzumab infusion. Circulating tumour cells assessments were added for the Phase II part. cfDNA tests and CTC tests were added to the criteria for efficacy section. Sample for future companion diagnostics development was included in the flowchart for Phase II part. Text was added to clarify that a central independent review of tumour images may be conducted at a later time. The benefit-risk assessment was improved by providing more detailed information. For the inclusion criteria, Criterion 4: "aged >=18 years old" was added to the criterion, and "women" was changed to "female patients". For the exclusion criteria, Criterion 2 was updated from: "Prior treatment with exemestane" To "Prior treatment with exemestane (except adjuvant exemestane stopped >12 months prior to start of study treatment as long as patient did not recur during or within 12 months after the end of adjuvant exemestane)", for consistency with clinical practice. Restrictions regarding concomitant treatment were updated reflect updates to the Afinitor SmPC and dose modification recommendations for exemestane were made according to EU label (US label information was taken out). Management of expected adverse events and management of infection text were updated in line with the updated Afinitor SmPC. DLT was deleted as an endpoint from the endpoints of safety section, as it is a formal endpoint.
30 March 2016	Corrections and clarifications were made. Inclusion Criterion 4 was reworded for consistency with current postmenopausal status definition at participating investigational sites. A recommendation to monitor weight loss was added. The following wording was added to improve accuracy of assessment of efficacy for these particular cases: "Patients who discontinue the trial for any reason other than imaging based progressive disease should have a tumour assessment (RECIST 1.1) performed at EOTV (exception to this are patients who have already had tumour assessment within 28 days of EOT visit)". Pneumonitis was added as an AESI to closely monitor these AEs. Phosphorus was added to the assessment of safety parameters based on the everolimus SmPC update. Definitions of the primary and secondary endpoints were updated in line with BI standards. The changes were to wording; there were no changes regarding content. Exemptions to SAE reporting were added. PD is already reported as a clinical trial endpoint and therefore does not need to be reported as an (S)AE. This is the common procedure in most oncology trials. Further endpoints for the Phase Ib part were added. Derivation of PFS and censoring rules were added in line with BI standards. More detailed description of the two prespecified analyses performed by the DMC were added.

15 December 2016	On 18 Oct 2016, the DMC had the meeting for the pre-specified interim analysis of efficacy after 33% of the required number of outcome events had been reached. At that time, 32 patients in the Xe1000+Ev10+Ex25 arm and 36 patients in the control arm were still on randomised treatment. The DMC recommendation letter was received on 20 Oct 2016, in which they recommended terminating the trial for the following reasons: the benefit-risk balance of xentuzumab in combination with exemestane and everolimus was no longer favourable for patients with HR+/HER2– locally advanced or metastatic breast cancer. The change in benefit-risk balance was a result of lack of efficacy; there were no important differences in safety between treatment arms. The DMC recommendation was evaluated by the benefit risk evaluation committee (BREC), and a decision was taken on 25 Oct 2016 to discontinue administration of xentuzumab permanently in the 1280.4 study. BI informed the investigators, ethics committees, and health authorities of the decision to discontinue xentuzumab treatment in trial 1280.4 on 28 Oct 2016. Further enrolment was terminated; however, the trial itself was not to be terminated. An exception was provided only for the patient ongoing in the Phase Ib part of the study. This patient experienced a partial response, had been on therapy for more than 20 months and no remarkable safety issues had been identified. The duration of response for this patient was also considered exceptional relative to published historical information for the background therapy (everolimus + exemestane). Only after reconsenting was the patient allowed to remain on treatment under the supervision of the treating physician. At the time of writing this CTR, this patient has been on treatment with xentuzumab + everolimus + exemestane for more than 42 months.
15 December 2016	Amendment 3 continued: Amendment 3 was implemented to reflect the sponsor decision to discontinue xentuzumab on 28 Oct 2016. The amendment introduced several changes as a result of the discontinuation of xentuzumab including: Termination of the collection of samples for pharmacokinetics, biomarkers, circulating tumour cells and antidrug antibodies, after xentuzumab was discontinued. Safety lab and ECGs were to be performed as indicated in the approved label of everolimus / exemestane or according local practice after xentuzumab discontinuation. A new flowchart for the Phase II part was added. Clarified that blinding of the project team could no longer remain after xentuzumab discontinuation. Clarification than despite xentuzumab discontinuation, patients could continue on everolimus and exemestane. Added that cfDNA is obtained at the time of xentuzumab discontinuation for patients in the experimental arm. Clarification that analysis after 90 PFS events made no sense after the xentuzumab discontinuation. The analyses for the primary endpoint were to be done with data obtained up to 4 weeks after xentuzumab discontinuation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Xentuzumab (Xen) stopped per sponsor decision 28Oct2016; patients (p) could continue with everolimus+exemestane. P attend for an end of Xen visit (EoXV, same procedures as end of trial visit). Recruitment stopped but study completed per protocol.

Notes: