



Clinical trial results:

Xenera™ 1: A multi-centre, double-blind, placebo-controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in women with HR+ / HER2- metastatic breast cancer and non-visceral disease

Summary

EudraCT number	2017-003131-11
Trial protocol	DE BE ES GR PT GB IT
Global end of trial date	11 May 2022

Results information

Result version number	v1 (current)
This version publication date	11 May 2023
First version publication date	11 May 2023

Trial information

Trial identification

Sponsor protocol code	1280-0022
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03659136
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 Centre, Boehringer Ingelheim, 001 018002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 001 018002430127, 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	29 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2021
Global end of trial reached?	Yes
Global end of trial date	11 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the efficacy of xentuzumab in combination with everolimus and exemestane over everolimus and exemestane in patients with HR+/HER2- advanced or metastatic breast cancer and non-visceral disease.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2019
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	Australia: 4
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	148
EEA total number of subjects	101

Notes:

Subjects enrolled per age group

In utero	0
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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)	95
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A multi-centre, double-blind, placebo-controlled, randomised trial which assess the efficacy of of xentuzumab in combination with everolimus and exemestane over everolimus and exemestane in patients with Hormon Receptor+ (HR+)/ Human epidermal growth factor receptor 2 (HER2)- advanced or metastatic breast cancer and non-visceral disease.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

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

Blinding implementation details:

Double-blind design. The randomisation code was kept secret by Clinical Trial Support up to database lock. At that time, the database was unblinded for analysis and reporting. The independent data monitoring committee had access to the unblinded treatment codes to allow them to periodically assess the trial data to ensure the overall safety and integrity of the trial, as well as to conduct the prespecified Phase II primary progression-free survival analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane

Arm description:

1000 mg concentrate for solution for infusion of Xentuzumab (BI 836845) (10mg/mL supplied in 20mL vials (200mg/vial)) was administered once weekly as intravenous infusion over 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles and tablets of 10 mg of Everolimus (Afinitor®) and tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day at approximately the same time of day, after a meal.

Arm type	Experimental
Investigational medicinal product name	Xentuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg concentrate for solution for infusion of Xentuzumab (BI 836845) (10mg/mL supplied in 20mL vials (200mg/vial)) was administered once weekly as intravenous infusion over 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles.

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

Dosage and administration details:

Tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day after a meal.

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

Dosage and administration details:

Tablets of 10 mg of Everolimus (Afinitor®) were administered orally once per day after a meal.

Arm title	Placebo + 10 mg everolimus + 25 mg exemestane
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Arm description:

Concentrate for solution for infusion of Placebo was administered once weekly as intravenous infusion of 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles and tablets of 10 mg of Everolimus (Afinitor®) and tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day at approximately the same time of day, after a meal.

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

Dosage and administration details:

Concentrate for solution for infusion of Placebo was administered once weekly as intravenous infusion of 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles.

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

Dosage and administration details:

Tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day after a meal.

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

Dosage and administration details:

Tablets of 10 mg of Everolimus (Afinitor®) were administered orally once per day after a meal.

Number of subjects in period 1^[1]	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	Placebo + 10 mg everolimus + 25 mg exemestane
Started	52	51
Treated	50	51
On-treatment, cut-off date(pr. analysis)	9	12
Completed	0	0
Not completed	52	51
Sponsor decision/recommendation	3	2
Adverse Event	4	6

Covid-19 related	1	1
Switched to other drug/therapy	2	2
Lack of clinical benefit	-	1
Progressive disease	37	31
Not treated	2	-
Withdrawal by subject	1	6
Study closure	2	2

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: 148 patients were enrolled worldwide, whereof 103 subjects actually started in the trial.

Baseline characteristics

Reporting groups

Reporting group title	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane
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Reporting group description:

1000 mg concentrate for solution for infusion of Xentuzumab (BI 836845) (10mg/mL supplied in 20mL vials (200mg/vial)) was administered once weekly as intravenous infusion over 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles and tablets of 10 mg of Everolimus (Afinitor®) and tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day at approximately the same time of day, after a meal.

Reporting group title	Placebo + 10 mg everolimus + 25 mg exemestane
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Reporting group description:

Concentrate for solution for infusion of Placebo was administered once weekly as intravenous infusion of 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles and tablets of 10 mg of Everolimus (Afinitor®) and tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day at approximately the same time of day, after a meal.

Reporting group values	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	Placebo + 10 mg everolimus + 25 mg exemestane	Total
Number of subjects	52	51	103
Age categorical			
Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.			
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)	32	31	63
From 65-84 years	20	20	40
85 years and over	0	0	0
Age Continuous			
Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.			
Units: years			
arithmetic mean	60.9	60.3	-
standard deviation	± 11.3	± 9.6	-
Sex: Female, Male			
Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.			
Units: Participants			
Female	52	51	103
Male	0	0	0
Ethnicity (NIH/OMB)			
Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.			
Units: Subjects			

Hispanic or Latino	3	2	5
Not Hispanic or Latino	43	41	84
Unknown or Not Reported	6	8	14
Race (NIH/OMB)			
Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	0	1	1
White	44	41	85
More than one race	0	0	0
Unknown or Not Reported	6	9	15

End points

End points reporting groups

Reporting group title	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane
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Reporting group description:

1000 mg concentrate for solution for infusion of Xentuzumab (BI 836845) (10mg/mL supplied in 20mL vials (200mg/vial)) was administered once weekly as intravenous infusion over 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles and tablets of 10 mg of Everolimus (Afinitor®) and tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day at approximately the same time of day, after a meal.

Reporting group title	Placebo + 10 mg everolimus + 25 mg exemestane
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Reporting group description:

Concentrate for solution for infusion of Placebo was administered once weekly as intravenous infusion of 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles and tablets of 10 mg of Everolimus (Afinitor®) and tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day at approximately the same time of day, after a meal.

Primary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
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End point description:

Progression-free survival (PFS) defined as the time from randomisation until progressive disease (PD) according to Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1) in combination with modified MD Anderson Criteria (for bone lesion assessment), based on blinded independent assessment or death from any cause, whichever occurred earlier. As per RECIST, PD is defined as at least a 20% increase in the sum of diameters of target lesions, unequivocal progression of non-target lesions or the appearance of new lesions.

Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.

End point type	Primary
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End point timeframe:

From randomisation until the earliest of disease progression, death or the time point of primary PFS analysis, up to 892 days.

End point values	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	Placebo + 10 mg everolimus + 25 mg exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Months				
median (confidence interval 95%)	12.7 (6.8 to 29.3)	11.0 (7.7 to 19.5)		

Statistical analyses

Statistical analysis title	Cox proportional hazard model
Statistical analysis description: Cox proportional hazards model stratified for presence of baseline bone-only metastases, prior cyclin-dependent kinase (CDK) 4/6 inhibitor treatment and menopause status.	
Comparison groups	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane v Placebo + 10 mg everolimus + 25 mg exemestane
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6534
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.59

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description: Overall survival (OS) defined as the time from randomisation until death from any cause. For patients with 'event' as an outcome for OS: OS[days] = date of outcome - date of randomisation + 1. For patients with 'censored' as an outcome for OS: OS (censored)[days] = date of outcome - date of randomisation + 1. Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not. 99999 is Not Applicable (NA) value. Median and upper bound of 95% CI could not be estimated due to insufficient events and data immaturity.	
End point type	Secondary
End point timeframe: From randomisation until death from any cause, up to 995 days.	

End point values	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	Placebo + 10 mg everolimus + 25 mg exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Months				
median (confidence interval 95%)	99999 (22.3 to 99999)	99999 (22.3 to 99999)		

Statistical analyses

Statistical analysis title	Cox proportional hazard model
Statistical analysis description: Cox proportional hazards model stratified for presence of baseline bone-only metastases, prior cyclin-dependent kinase (CDK) 4/6 inhibitor treatment and menopause status.	
Comparison groups	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane v Placebo + 10 mg everolimus + 25 mg exemestane
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1797
Method	Log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	1.4

Secondary: Number of patients with disease control (DC)

End point title	Number of patients with disease control (DC)
End point description: Disease control (DC) was defined as a best overall response (BOR) of either complete response (CR), partial response (PR), stable disease (SD) or Non-CR/No-PD. SD and Non-CR/Non-PR must have been observed up until at least week 24 tumor assessment. BOR was defined according to RECIST v1.1 in combination with modified MD Anderson Criteria (for bone lesion assessment) based on all evaluable tumor assessments from randomisation until the earliest of PD, start of subsequent anti-cancer therapy, loss to follow-up, withdrawal of consent or death. To be aligned with the primary endpoint derivation, tumor assessments after two or more consecutively misses assessments were not considered. DC was assessed by independent reviewers. Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.	
End point type	Secondary
End point timeframe: From randomisation until the earliest of progressive disease or death from any cause, up to 892 days.	

End point values	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	Placebo + 10 mg everolimus + 25 mg exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Participants	29	25		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane v Placebo + 10 mg everolimus + 25 mg exemestane
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4932
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.86

Secondary: Duration of disease control (DC)

End point title	Duration of disease control (DC)
End point description:	
Duration of disease control (DC), defined as the time from randomisation until the earliest of disease progression (according to Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1) in combination with modified MD Anderson Criteria (for bone lesion assessment) or death from any cause, among patients with DC. Duration of DC was assessed by independent reviewers.	
The duration of DC was calculated as followed:	
For patients with disease progression or death:	
Duration of DC [days] = date of outcome – date of randomisation + 1	
For patients without disease progression or death:	
Duration of DC (censored) [days] = date of outcome – date of randomisation + 1	
Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not. Only participants with disease control are reported.	
99999 is Not Applicable (NA) value. Upper bound of 95% CI could not be estimated due to insufficient events and data immaturity.	
End point type	Secondary
End point timeframe:	
From randomisation until the earliest of progressive disease or death from any cause, up to 892 days.	

End point values	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	Placebo + 10 mg everolimus + 25 mg exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: Months				
median (confidence interval 95%)	14.6 (9.2 to 29.3)	18.4 (9.2 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Objective response (OR)

End point title	Number of participants with Objective response (OR)
End point description: Number of participants with objective response (OR) by independent assessment. OR is defined as a best overall response of complete response (CR) or partial response (PR). Best overall response is defined according to RECIST v1.1 in combination with modified MD Anderson Criteria (for bone lesion assessment) and will consider all tumor assessments from randomisation until the earliest of PD, start of subsequent anti-cancer therapy, loss to follow-up, withdrawal of consent or death. To be aligned with the primary endpoint derivation, tumor assessments after two or more consecutively misses assessments were not considered. Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not. Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.	
End point type	Secondary
End point timeframe: From randomisation until end of treatment, up to 892 days.	

End point values	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	Placebo + 10 mg everolimus + 25 mg exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Participants	6	5		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane v Placebo + 10 mg everolimus + 25 mg exemestane
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7759
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	4.43

Secondary: Time to pain progression or intensification of pain palliation

End point title	Time to pain progression or intensification of pain palliation
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End point description:

Time to pain progression or intensification of pain palliation was defined as the time from randomisation until the earliest of:

≥2 point increase from baseline in the Brief Pain Inventory – Short Form (BPI-SF), Item 3 (worst pain), without a decrease (of ≥1 point) from baseline analgesics use (via the 8-point Analgesic Quantification Algorithm [AQA]), or

≥2 point increase from baseline in the AQA, or Death.

Randomised Set (RS): The randomised set included all randomised patients, regardless of whether they received treatment or not.

99999 is Not Applicable (NA) value. Upper bound of 95% CI could not be estimated due to insufficient events and data immaturity.

End point type	Secondary
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End point timeframe:

From randomisation until the earliest of pain progression, intensification of pain palliation, death or the time point of progression free survival analysis, up to 843 days.

End point values	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	Placebo + 10 mg everolimus + 25 mg exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Months				
median (confidence interval 95%)	5.6 (3.2 to 9.3)	3.0 (1.9 to 99999)		

Statistical analyses

Statistical analysis title	Cox proportional hazard model
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Statistical analysis description:

Cox proportional hazards model stratified for presence of baseline bone-only metastases, prior cyclin-dependent kinase (CDK) 4/6 inhibitor treatment and menopause status.

Comparison groups	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane v Placebo + 10 mg everolimus + 25 mg exemestane
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Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9279
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.76

Adverse events

Adverse events information

Timeframe for reporting adverse events:

[All-cause mortality]: From signing informed consent until end of study, up to 1106 days.

[Serious and other AEs]: From first drug administration until end of treatment+42 days of residual effect period, up to 939 days.

Adverse event reporting additional description:

[All-cause mortality]: Randomised Set (RS). The actual number of participants at risk for all-cause death is 52 for Xentuzumab arm.

[Serious and other adverse events]: Treated Set (TS) including all patients who are documented to have received and taken at least one dose of any study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo + 10 mg everolimus + 25 mg exemestane
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Reporting group description:

Concentrate for solution for infusion of Placebo was administered once weekly as intravenous infusion of 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles and tablets of 10 mg of Everolimus (Afinitor®) and tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day at approximately the same time of day, after a meal.

Reporting group title	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane
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Reporting group description:

1000 mg concentrate for solution for infusion of Xentuzumab (BI 836845) (10mg/mL supplied in 20mL vials (200mg/vial)) was administered once weekly as intravenous infusion over 1 hour on day 1, 8, 15 and 22 of 28-days cycles and on day 1, 8, 15, 22, 29, 36, 43 and 50 of 56-day cycles and tablets of 10 mg of Everolimus (Afinitor®) and tablets of 25 mg Exemestane (Aromasin®) were administered orally once per day at approximately the same time of day, after a meal.

Serious adverse events	Placebo + 10 mg everolimus + 25 mg exemestane	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 51 (35.29%)	13 / 50 (26.00%)	
number of deaths (all causes)	10	6	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Oophorectomy bilateral			

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	3 / 51 (5.88%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lethargy			

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland calculus			

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dysuria			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Micturition urgency			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Tenosynovitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteonecrosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue abscess			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + 10 mg everolimus + 25 mg exemestane	1000 mg Xentuzumab + 10 mg everolimus + 25 mg exemestane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 51 (98.04%)	48 / 50 (96.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 51 (15.69%)	6 / 50 (12.00%)	
occurrences (all)	18	6	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	17 / 51 (33.33%)	15 / 50 (30.00%)	
occurrences (all)	31	24	
Influenza like illness			
subjects affected / exposed	3 / 51 (5.88%)	5 / 50 (10.00%)	
occurrences (all)	3	8	
Fatigue			
subjects affected / exposed	17 / 51 (33.33%)	22 / 50 (44.00%)	
occurrences (all)	24	35	
Chest pain			
subjects affected / exposed	4 / 51 (7.84%)	3 / 50 (6.00%)	
occurrences (all)	7	3	
Asthenia			
subjects affected / exposed	13 / 51 (25.49%)	10 / 50 (20.00%)	
occurrences (all)	22	20	

Oedema peripheral subjects affected / exposed occurrences (all)	9 / 51 (17.65%) 16	4 / 50 (8.00%) 6	
Pain subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6	3 / 50 (6.00%) 3	
Pyrexia subjects affected / exposed occurrences (all)	9 / 51 (17.65%) 9	7 / 50 (14.00%) 7	
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	3 / 50 (6.00%) 8	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	8 / 51 (15.69%) 9	13 / 50 (26.00%) 17	
Dysphonia subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 50 (0.00%) 0	
Dyspnoea subjects affected / exposed occurrences (all)	8 / 51 (15.69%) 12	8 / 50 (16.00%) 9	
Epistaxis subjects affected / exposed occurrences (all)	8 / 51 (15.69%) 11	15 / 50 (30.00%) 16	
Nasal dryness subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	3 / 50 (6.00%) 3	
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	5 / 50 (10.00%) 5	
Pleural effusion subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	3 / 50 (6.00%) 3	
Pneumonitis			

subjects affected / exposed occurrences (all)	13 / 51 (25.49%) 20	5 / 50 (10.00%) 6	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 51 (9.80%)	2 / 50 (4.00%)	
occurrences (all)	6	3	
Depression			
subjects affected / exposed	3 / 51 (5.88%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Insomnia			
subjects affected / exposed	5 / 51 (9.80%)	7 / 50 (14.00%)	
occurrences (all)	5	8	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	6 / 51 (11.76%)	4 / 50 (8.00%)	
occurrences (all)	19	10	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 51 (13.73%)	8 / 50 (16.00%)	
occurrences (all)	23	20	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 51 (15.69%)	5 / 50 (10.00%)	
occurrences (all)	21	9	
Blood albumin decreased			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Blood calcium decreased			
subjects affected / exposed	0 / 51 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Blood cholesterol increased			
subjects affected / exposed	3 / 51 (5.88%)	4 / 50 (8.00%)	
occurrences (all)	3	11	
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 51 (7.84%)	7 / 50 (14.00%)	
occurrences (all)	17	11	
Blood creatinine increased			

subjects affected / exposed	3 / 51 (5.88%)	5 / 50 (10.00%)	
occurrences (all)	3	11	
Blood glucose increased			
subjects affected / exposed	1 / 51 (1.96%)	4 / 50 (8.00%)	
occurrences (all)	1	4	
Blood lactate dehydrogenase increased			
subjects affected / exposed	7 / 51 (13.73%)	2 / 50 (4.00%)	
occurrences (all)	8	2	
Blood triglycerides increased			
subjects affected / exposed	0 / 51 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	12	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 51 (7.84%)	6 / 50 (12.00%)	
occurrences (all)	7	10	
Glycosylated haemoglobin increased			
subjects affected / exposed	3 / 51 (5.88%)	5 / 50 (10.00%)	
occurrences (all)	4	8	
Lymphocyte count decreased			
subjects affected / exposed	2 / 51 (3.92%)	3 / 50 (6.00%)	
occurrences (all)	2	4	
Platelet count decreased			
subjects affected / exposed	5 / 51 (9.80%)	9 / 50 (18.00%)	
occurrences (all)	5	19	
Weight decreased			
subjects affected / exposed	5 / 51 (9.80%)	7 / 50 (14.00%)	
occurrences (all)	6	9	
White blood cell count decreased			
subjects affected / exposed	3 / 51 (5.88%)	2 / 50 (4.00%)	
occurrences (all)	8	7	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 51 (5.88%)	7 / 50 (14.00%)	
occurrences (all)	4	9	
Fall			

subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	3 / 50 (6.00%) 4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 51 (7.84%)	9 / 50 (18.00%)	
occurrences (all)	4	11	
Dysgeusia			
subjects affected / exposed	6 / 51 (11.76%)	10 / 50 (20.00%)	
occurrences (all)	7	13	
Headache			
subjects affected / exposed	12 / 51 (23.53%)	20 / 50 (40.00%)	
occurrences (all)	21	26	
Paraesthesia			
subjects affected / exposed	4 / 51 (7.84%)	6 / 50 (12.00%)	
occurrences (all)	5	7	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Tremor			
subjects affected / exposed	1 / 51 (1.96%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Sciatica			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	5	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 51 (1.96%)	11 / 50 (22.00%)	
occurrences (all)	7	18	
Anaemia			
subjects affected / exposed	13 / 51 (25.49%)	10 / 50 (20.00%)	
occurrences (all)	28	27	
Neutropenia			
subjects affected / exposed	3 / 51 (5.88%)	9 / 50 (18.00%)	
occurrences (all)	5	14	
Ear and labyrinth disorders			

<p>Ear pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 51 (0.00%)</p> <p>0</p>	<p>3 / 50 (6.00%)</p> <p>4</p>	
<p>Vertigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 51 (3.92%)</p> <p>2</p>	<p>5 / 50 (10.00%)</p> <p>6</p>	
<p>Eye disorders</p> <p>Lacrimation increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry eye</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 51 (1.96%)</p> <p>1</p> <p>3 / 51 (5.88%)</p> <p>3</p>	<p>3 / 50 (6.00%)</p> <p>3</p> <p>5 / 50 (10.00%)</p> <p>5</p>	
<p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspepsia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry mouth</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Toothache</p>	<p>3 / 51 (5.88%)</p> <p>7</p> <p>3 / 51 (5.88%)</p> <p>3</p> <p>8 / 51 (15.69%)</p> <p>10</p> <p>4 / 51 (7.84%)</p> <p>4</p> <p>9 / 51 (17.65%)</p> <p>9</p> <p>17 / 51 (33.33%)</p> <p>47</p> <p>8 / 51 (15.69%)</p> <p>13</p>	<p>5 / 50 (10.00%)</p> <p>6</p> <p>4 / 50 (8.00%)</p> <p>4</p> <p>5 / 50 (10.00%)</p> <p>5</p> <p>7 / 50 (14.00%)</p> <p>7</p> <p>5 / 50 (10.00%)</p> <p>6</p> <p>28 / 50 (56.00%)</p> <p>48</p> <p>9 / 50 (18.00%)</p> <p>15</p>	

subjects affected / exposed	1 / 51 (1.96%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Stomatitis			
subjects affected / exposed	15 / 51 (29.41%)	14 / 50 (28.00%)	
occurrences (all)	29	23	
Oral pain			
subjects affected / exposed	1 / 51 (1.96%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	14 / 51 (27.45%)	18 / 50 (36.00%)	
occurrences (all)	23	28	
Haemorrhoids			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	4	0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 50 (0.00%)	
occurrences (all)	6	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 51 (17.65%)	13 / 50 (26.00%)	
occurrences (all)	18	18	
Pruritus			
subjects affected / exposed	9 / 51 (17.65%)	10 / 50 (20.00%)	
occurrences (all)	13	13	
Erythema			
subjects affected / exposed	2 / 51 (3.92%)	6 / 50 (12.00%)	
occurrences (all)	2	6	
Eczema			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	5	0	
Dry skin			
subjects affected / exposed	3 / 51 (5.88%)	6 / 50 (12.00%)	
occurrences (all)	3	7	
Alopecia			

subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	5 / 50 (10.00%) 5	
Dermatitis acneiform subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 5	4 / 50 (8.00%) 5	
Rash pruritic subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 6	0 / 50 (0.00%) 0	
Rash maculo-papular subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 3	3 / 50 (6.00%) 4	
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4	4 / 50 (8.00%) 5	
Pollakiuria subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	4 / 50 (8.00%) 4	
Proteinuria subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 9	1 / 50 (2.00%) 6	
Glycosuria subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4	0 / 50 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	17 / 51 (33.33%) 26	16 / 50 (32.00%) 25	
Back pain subjects affected / exposed occurrences (all)	9 / 51 (17.65%) 14	3 / 50 (6.00%) 4	
Bone pain subjects affected / exposed occurrences (all)	7 / 51 (13.73%) 10	4 / 50 (8.00%) 7	
Muscle spasms			

subjects affected / exposed	6 / 51 (11.76%)	12 / 50 (24.00%)	
occurrences (all)	8	17	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 51 (3.92%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Myalgia			
subjects affected / exposed	4 / 51 (7.84%)	6 / 50 (12.00%)	
occurrences (all)	5	9	
Neck pain			
subjects affected / exposed	4 / 51 (7.84%)	4 / 50 (8.00%)	
occurrences (all)	4	4	
Pain in extremity			
subjects affected / exposed	8 / 51 (15.69%)	7 / 50 (14.00%)	
occurrences (all)	11	12	
Pain in jaw			
subjects affected / exposed	1 / 51 (1.96%)	3 / 50 (6.00%)	
occurrences (all)	1	4	
Infections and infestations			
Cellulitis			
subjects affected / exposed	4 / 51 (7.84%)	1 / 50 (2.00%)	
occurrences (all)	4	1	
Gingivitis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Oral candidiasis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Tooth abscess			
subjects affected / exposed	4 / 51 (7.84%)	0 / 50 (0.00%)	
occurrences (all)	4	0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 51 (5.88%)	3 / 50 (6.00%)	
occurrences (all)	3	3	
Urinary tract infection			
subjects affected / exposed	9 / 51 (17.65%)	9 / 50 (18.00%)	
occurrences (all)	14	11	

COVID-19 subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 5	0 / 50 (0.00%) 0	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	18 / 51 (35.29%) 25	18 / 50 (36.00%) 29	
Dehydration subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	2 / 50 (4.00%) 2	
Hypercholesterolaemia subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 3	6 / 50 (12.00%) 10	
Hyperglycaemia subjects affected / exposed occurrences (all)	13 / 51 (25.49%) 24	10 / 50 (20.00%) 16	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 23	5 / 50 (10.00%) 7	
Hypocalcaemia subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	3 / 50 (6.00%) 4	
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	6 / 50 (12.00%) 6	
Hypophosphataemia subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6	4 / 50 (8.00%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2018	This amendment was made prior to first patient recruitment. Key provisions introduced by this amendment included (1) the trial was changed from Phase III to Phase II and associated changes were made in the number of trial sites, countries, patient numbers, statistical analyses, and biomarker sampling; (2) language was added to allow for seamless expansion to a Phase III trial if criteria were met; and (3) the patient reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaire was added to examine patient perception of adverse events (AEs).
14 February 2019	The protocol was amended based on feedback from investigators and to provide needed clarification. Key aspects of this amendment included (1) revised inclusion criterion 3 to state that biopsies could not be performed after consent for the purpose of the trial and that archival biopsy samples had to be provided to the sponsor; (2) exclusion criteria 22 was updated to include a washout period for any restricted medications; (3) withdrawal from trial treatment updated to state that if a patient required palliative radiotherapy, the patient would need to stop the trial; (4) screening period was increased from 14 to 28 days to allow additional time for screening procedures; (5) third party blinding added due to visual difference in appearance of placebo versus xentuzumab; (6) management of stomatitis/mucosal inflammation section updated to provide guidance regarding dexamethasone-containing mouthwashes; (7) addition of language that MD Anderson criteria would also be used in selection of target and or non-target lesions in the bone; (8) safety laboratory parameters section updated to include fasting requirements and to clarify that safety labs could be taken on the day before infusion as long as they were within clinical trial protocol (CTP) specified visit windows; (9) due to change in trial design (Phase III to Phase II), the interim analysis was removed, text was added stating that if the trial was seamlessly expanded to Phase III then end of Phase II would be considered as an interim analysis, and that the null hypothesis for primary analysis PFS was at end of Phase III.
30 July 2019	Key provisions of this amendment included: (1) inclusion/exclusion criteria adapted to allow use of original histology report if archival tissue not available, include premenopausal women on ovarian suppression and birth control rather than just post-menopausal women, to allow enrolment of patients with blastic lesions only, and to allow for additional prior therapy options including some endocrine therapies, Phosphatidylinositol 3-kinase (PI3K) therapy, and one line of chemotherapy; (2) menopause status was added as a stratification factor; and (3) given the inclusion of premenopausal women, ovarian suppression and monitoring was also included. Additionally, because the use of Ev/Ex in premenopausal women on ovarian suppression might be considered off-label in some countries, clarified that Ev/Ex are not considered as investigational in this trial; however, where local regulatory requirements mandate it, then it may be considered as Investigational medicinal product (IMP) and would be provided as labelled product to the sites.

05 February 2020	Key changes introduced by this amendment included: (1) increase in number of patients who could be recruited to a maximum of 100 to help achieve the required number of events; (2) inclusion/exclusion criteria updated to reflect amended contraception requirements for xentuzumab for women of childbearing potential, increased flexibility of study visits for patients who discontinued xentuzumab/placebo in order to help patient retention, and allowance of plasma to be used for biochemistry tests, if appropriate, in place of serum; and (3) updated language to allow for analysis of the Phase II trial without 40 progression-free survival (PFS) events with the condition that the trial would not be considered to have met criteria for seamless transition to Phase III.
25 November 2021	This amendment was introduced after unblinded top-line data review. Because the benefit-risk ratio was no longer favourable due to lack of xentuzumab efficacy, this amendment recommended xentuzumab/placebo discontinuation and an associated decrease in visits/assessments, retaining only those necessary for patient safety. A new patient visit/assessment flow chart was provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported