Clinical trial results:
Essai randomisé multicentrique de phase III comparant la poursuite du traitement d'entretien par l'association bevacizumab + taxane versus remplacement par bevacizumab + exemestane chez des patientes atteintes de cancer du sein métastatique ou localement avancé, avec des récepteurs aux estrogènes positifs et ayant au moins une stabilisation de la maladie après 16-18 semaines de traitement par bevacizumab + taxane.

Summary

EudraCT number	2009-016338-29
Trial protocol	FR
Global end of trial date	18 September 2018

Results information

Result version number	v1 (current)
This version publication date	02 June 2022
First version publication date	02 June 2022

Trial information

Trial identification

Sponsor protocol code	GINECO-BR107

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ARCAGY
Sponsor organisation address	1, place du Parvis Notre-Dame, HOPITAL HOTEL DIEU-B2 5ème étage, PARIS, France, 75181 cedex 4
Public contact	S. ARMANET, ARCAGY, reglementaire@arcagy.org
Scientific contact	Thomas BACHELOT , ARCAGY, bachelot@lyon.fnclcc.fr

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	12 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2018
Global end of trial reached?	Yes
Global end of trial date	18 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Comparer la survie sans progression entre l’association bevacizumab-hormonothérapie en traitement d’entretien (bras expérimental) et la poursuite de la chimiothérapie taxane-bevacizumab (bras contrôle)

Protection of trial subjects:

Cette étude a été menée selon les recommandations :

- de la loi Bioéthique n° 2004-800 du 6 août 2004;

- de la "Déclaration d'Helsinki" révisée à Washington en 2002, Octobre 2000

- des bonnes pratiques cliniques de la conférence internationale d’harmonisation (ICH-E6 du 17/07/1996);

- de la loi Huriet (n°88-1138) du 20 décembre 1988 relative à la Protection des Personnes se prêtant à la Recherche Biomédicale et modifiée par la loi de santé publique (n°2004-806) du 9 août 2004;

- de la loi Informatique et Libertés n°78-17 modifiée par la loi n° 2004-801 du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel;

- de la direction européenne (2001/20/CE) sur la conduite des essais cliniques

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 117
Worldwide total number of subjects	117
EEA total number of subjects	117

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)	92
From 65 to 84 years	24
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 141 events were required to have 90% power to show a statistically significant difference (2-sided alpha, using a log-rank test). Anticipating recruitment duration of 24 months and a 6-month follow-up for the last patient included, the estimated total duration of the study was 30 months, and 186 evaluable patients included

Pre-assignment

Screening details:

117 patients randomized between June 2010 and July 2013. Of the 117 patients, 59 were randomized to continue on their first
line regimen with taxane + bevacizumab and 58 were randomized to receive the combination
of exemestane + bevacizumab .

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bras A (expérimental)

Arm description:

bras expérimental

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	RO4876646
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

bevacizumab : 15 mg/kg every 3 weeks in IV

Investigational medicinal product name	Exemestane
Investigational medicinal product code	0009-6663
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg daily per os

Arm title	Bras B (contrôle)

Arm description:

bras contrôle

Arm type	Control
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	RO4876646
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks in IV

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

Dosage and administration details:
either paclitaxel 80-90 mg/m² for 3 weeks of a 4-week cycle

Number of subjects in period 1	Bras A (expérimental)	Bras B (contrôle)
Started	58	59
Completed	58	59

Baseline characteristics

Reporting groups	
Reporting group title	Bras A (expérimental)
Reporting group description: bras expérimental	
Reporting group title	Bras B (contrôle)
Reporting group description: bras contrôle	

Reporting group values	Bras A (expérimental)	Bras B (contrôle)	Total
Number of subjects	58	59	117
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	56.5	56.0	
full range (min-max)	35 to 77	35 to 86	-
Gender categorical Units: Subjects			
Female	58	59	117

Subject analysis sets	
Subject analysis set title	Bras expérimental
Subject analysis set type	Full analysis
Subject analysis set description: Association d’exemestane (Aromasine®) à 25 mg/j per os et de bevacizumab à 15 mg/kg en I.V. à J1 toutes les 3 semaines.	
Subject analysis set title	Bras contrôle
Subject analysis set type	Full analysis
Subject analysis set description: Poursuite de l’association paclitaxel et de bevacizumab en I.V. à J1 à 10 mg/kg toutes les 2 semaines OU à 15 mg/kg toutes les 3 semaines. Dans le bras contrôle, le bevacizumab a dû être administré avant la chimiothérapie	

Reporting group values	Bras expérimental	Bras contrôle	
Number of subjects	58	59	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	56.5	56.0	
full range (min-max)	35 to 77	35 to 86	
Gender categorical Units: Subjects			
Female			

End points

End points reporting groups

Reporting group title	Bras A (expérimental)
Reporting group description: bras expérimental	
Reporting group title	Bras B (contrôle)
Reporting group description: bras contrôle	
Subject analysis set title	Bras expérimental
Subject analysis set type	Full analysis
Subject analysis set description: Association d'exemestane (Aromasine®) à 25 mg/j per os et de bevacizumab à 15 mg/kg en I.V. à J1 toutes les 3 semaines.	
Subject analysis set title	Bras contrôle
Subject analysis set type	Full analysis
Subject analysis set description: Poursuite de l'association paclitaxel et de bevacizumab en I.V. à J1 à 10 mg/kg toutes les 2 semaines OU à 15 mg/kg toutes les 3 semaines. Dans le bras contrôle, le bevacizumab a dû être administré avant la chimiothérapie	

Primary: Progression Free Survival (6-month rate)

End point title	Progression Free Survival (6-month rate)
End point description:	
End point type	Primary
End point timeframe: The primary endpoint of the study, PFS, was defined as the time from randomization to the first investigator-assessed progression, or death irrespective of the underlying cause.	

End point values	Bras A (expérimental)	Bras B (contrôle)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: percent				
number (confidence interval 95%)	55.2 (41.5 to 66.9)	67.2 (53.6 to 77.7)		

Statistical analyses

Statistical analysis title	Survival analyses

Statistical analysis description:

Survival data were estimated using the Kaplan-Meier method, and the log-rank test was used to compare the survival curves of the 2 study arms. A Cox proportional hazards model was used to estimate the HR with 95% CIs.

A total of 141 PFS events were required to have 90% power to show a statistically significant difference (2-sided alpha, using a log-rank test).

Comparison groups	Bras A (expérimental) v Bras B (contrôle)
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.998 [2]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.51

Notes:

[1] - Boundary significance levels of 0.001 and 0.049 were used at the interim and final analyses, respectively, to test the superiority of PFS in the experimental arm
[2] - there is no evidence of significant difference between the two arms

Primary: Progression Free Survival (median)

End point title	Progression Free Survival (median)[3]

End point description:

End point type	Primary

End point timeframe:

The primary endpoint of the study, PFS, was defined as the time from randomization to the first investigator-assessed progression, or death irrespective of the underlying cause.

Notes:

[3] - 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: We made statistical analysis for Progression Free Survival (6-month rate) not for Progression Free Survival (median)

End point values	Bras A (expérimental)	Bras B (contrôle)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	59		
Units: month				
median (confidence interval 95%)	7.6 (5.4 to 10.9)	8.1 (6.5 to 10.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Every visites	
Adverse event reporting additional description:	
All randomized patients were analyzed for safety, Adverse Event were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	Bras A
Reporting group description:	
bras expérimental	
Reporting group title	Bras B
Reporting group description:	
bras contrôle	

Serious adverse events	Bras A	Bras B	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 58 (29.31%)	19 / 59 (32.20%)	
number of deaths (all causes)	19	16	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hypercalcaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
WORSENING OF METASTASIS OF THE RIGHT FEMORAL NECK			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Myocardial infarction			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 58 (3.45%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Angioplasty			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
degrade of general status			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
LEFT Breast inflammation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
BASAL RIGHT PNEUMOPATHY			

subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
FEVG decrease			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Device dislocation			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC DRUG			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
NEUROPATHY			
subjects affected / exposed	0 / 58 (0.00%)	11 / 59 (18.64%)	
occurrences causally related to treatment / all	0 / 0	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile aplasia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bilirubin increased			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISTURBANCE IN HEPATIC BALANCE			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Onycholysis			

subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOE UNGEOPATHY			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL INSUFFICIENCY			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR NECK FRACTURE			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT PAIN			
subjects affected / exposed	1 / 58 (1.72%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Infection			
subjects affected / exposed	1 / 58 (1.72%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Deficiency anaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	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	Bras A	Bras B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 58 (100.00%)	59 / 59 (100.00%)	
Investigations			
Creatinine increased	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	12 / 58 (20.69%)	8 / 59 (13.56%)	
occurrences (all)	12	8	
Bilirubin increased	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	12 / 58 (20.69%)	8 / 59 (13.56%)	
occurrences (all)	12	8	
SGOT INCREASED	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	35 / 58 (60.34%)	38 / 59 (64.41%)	
occurrences (all)	35	38	
SGPT Increased	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	25 / 58 (43.10%)	30 / 59 (50.85%)	
occurrences (all)	25	30	
Phosphatase alcaline SAI augmentée	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		

subjects affected / exposed	24 / 58 (41.38%)	26 / 59 (44.07%)	
occurrences (all)	24	26	
CALCIUM INCREASED	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	14 / 58 (24.14%)	9 / 59 (15.25%)	
occurrences (all)	14	9	
GLYCEMIE INCREASED	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	18 / 58 (31.03%)	19 / 59 (32.20%)	
occurrences (all)	18	19	
TRIGLYCERIDE INCREASED	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	19 / 58 (32.76%)	19 / 59 (32.20%)	
occurrences (all)	19	19	
CHOLESTEROL INCREASED	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	29 / 58 (50.00%)	29 / 59 (49.15%)	
occurrences (all)	29	29	
Cardiac disorders			
Hypertension	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	53 / 58 (91.38%)	54 / 59 (91.53%)	
occurrences (all)	53	54	
Hemorragie	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	14 / 58 (24.14%)	23 / 59 (38.98%)	
occurrences (all)	14	23	
THROMBO EMBOLIE	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	3 / 58 (5.17%)	3 / 59 (5.08%)	
occurrences (all)	3	3	
Nervous system disorders			
Peripheral sensory neuropathy	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	19 / 58 (32.76%)	39 / 59 (66.10%)	
occurrences (all)	19	39	
Neuropathie motrice	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	5 / 58 (8.62%)	9 / 59 (15.25%)	
occurrences (all)	5	9	
Blood and lymphatic system disorders			
Anaemia	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		

subjects affected / exposed	22 / 58 (37.93%)	34 / 59 (57.63%)	
occurrences (all)	22	34	
Neutropenia	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	15 / 58 (25.86%)	35 / 59 (59.32%)	
occurrences (all)	15	35	
Lymphopenia	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	18 / 58 (31.03%)	28 / 59 (47.46%)	
occurrences (all)	18	28	
Thrombocytopenia	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	3 / 58 (5.17%)	4 / 59 (6.78%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Fatigue	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	30 / 58 (51.72%)	47 / 59 (79.66%)	
occurrences (all)	30	47	
Pain	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	38 / 58 (65.52%)	42 / 59 (71.19%)	
occurrences (all)	38	42	
FEVER	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	1 / 58 (1.72%)	9 / 59 (15.25%)	
occurrences (all)	1	9	
Gastrointestinal disorders			
Nausea	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	14 / 58 (24.14%)	18 / 59 (30.51%)	
occurrences (all)	14	18	
Vomiting	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	11 / 58 (18.97%)	3 / 59 (5.08%)	
occurrences (all)	11	3	
Constipation	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	6 / 58 (10.34%)	12 / 59 (20.34%)	
occurrences (all)	6	12	
Diarrhea	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		

subjects affected / exposed	10 / 58 (17.24%)	10 / 59 (16.95%)	
occurrences (all)	10	10	
Mucite orale	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	4 / 58 (6.90%)	9 / 59 (15.25%)	
occurrences (all)	4	9	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	17 / 58 (29.31%)	35 / 59 (59.32%)	
occurrences (all)	17	35	
Nail disorder	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	9 / 58 (15.52%)	26 / 59 (44.07%)	
occurrences (all)	9	26	
Oedema	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	10 / 58 (17.24%)	16 / 59 (27.12%)	
occurrences (all)	10	16	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	25 / 58 (43.10%)	18 / 59 (30.51%)	
occurrences (all)	25	18	
Myalgie	Additional description: Occurrences all number is not calculated, we reported the Subjects affected number in place		
subjects affected / exposed	7 / 58 (12.07%)	16 / 59 (27.12%)	
occurrences (all)	7	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported