Clinical trial results:
Phase II trial of trastuzumab in combination with pertuzumab in pretreated patients with non-small cell lung cancer (NSCLC) harboring a Her2 mutation and receiving docetaxel

Summary

EudraCT number	2018-003506-11
Trial protocol	FR
Global end of trial date	18 December 2023

Results information

Result version number	v1 (current)
This version publication date	18 January 2025
First version publication date	18 January 2025

Trial information

Trial identification

Sponsor protocol code	IFCT-1703

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03845270
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 rue de la Grange-Batelière, Paris, France, 75009
Public contact	Contact, IFCT, 33 156811045, operations-cliniques@ifct.fr
Scientific contact	Contact, IFCT, 33 156811045, operations-cliniques@ifct.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	31 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2020
Global end of trial reached?	Yes
Global end of trial date	18 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy of trastuzumab in combination with pertuzumab and docetaxel in patients with HER2 mutated advanced NSCLC

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	23
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From May 2019 to October 2020, 47 patients were screened; 46 patients were initially included (one was deemed ineligible because of a poor performance status), and 45 patients were enrolled and received the study treatment.

Pre-assignment

Screening details:

Main inclusion criteria were histologically/cytologically confirmed inoperable and not suitable for radiation stage III or stage IV nonsquamous NSCLC with HER2 alterations. Other inclusion criteria were pretreatment with at least one platinum-based therapy with documented disease progression, the presence of asymptomatic or treated brain metastases

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Arm title	Pertuzumab - Trastuzumab - Docetaxel

Arm description:

Pertuzumab was administered as an intravenous (IV) loading dose of 840 mg once every 3 weeks on day 1 of cycle 1 (1 cycle length 5 21 days), and 420 mg once every 3 weeks on day 1 of subsequent cycles. Trastuzumab was
administered as an IV loading dose of 8 milligrams per kilogram (mg/kg) once every 3 weeks on day 2 of cycle 1 (1 cycle length 5 21 days), and 6 mg/kg once every 3 weeks on day 1 of subsequent cycles. Docetaxel was administered as an IV dose of 75 milligrams per square meter of body surface area (mg/m2) once every 3 weeks on day 2 of cycle 1 (1 cycle length 5 21 days), and 75 mg/m2 once every 3 weeks on day 1 of subsequent cycles. Treatment was given until toxicity or disease progression.

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

Dosage and administration details:

Pertuzumab was administered as an intravenous (IV) loading dose of 840 mg once every 3 weeks on day 1 of cycle 1 (1 cycle length 5 21 days), and 420 mg once every 3 weeks on day 1 of subsequent cycles. .

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered as an IV loading dose of 8 milligrams per kilogram (mg/kg) once every 3 weeks on day 2 of cycle 1 (1 cycle length 5 21 days), and 6 mg/kg once every 3 weeks on day 1 of subsequent cycles.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel was administered as an IV dose of 75 milligrams per square meter of body surface area (mg/m2) once every 3 weeks on day 2 of cycle 1 (1 cycle length 5 21 days), and 75 mg/m2 once every 3 weeks on day 1 of subsequent cycles.

Number of subjects in period 1	Pertuzumab - Trastuzumab - Docetaxel
Started	46
Completed	45
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	46	46	
Age categorical 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)	23	23	
From 65-84 years	23	23	
85 years and over	0	0	
Age continuous Units: years			
median	64.5		
full range (min-max)	31 to 83.7	-	
Gender categorical Units: Subjects			
Female	33	33	
Male	13	13	
Smokers Units: Subjects			
Yes	16	16	
No	30	30	
NSCLC histologically confirmed Units: Subjects			
Yes	45	45	
No	1	1	
NSCLC cytologically confirmed Units: Subjects			
Yes	24	24	
No	19	19	
Unknown	3	3	
Histological type Units: Subjects			
Adenocarcinoma	46	46	
Number of prior lines			
The lines are counted based on interval disease progression and not the number of agents or switches in agents			
Units: Subjects			

One	34	34	
Two	10	10	
Three or more	2	2	
TNM Units: Subjects			
IIIB	4	4	
IVA	9	9	
IVB	33	33	
PS Units: Subjects			
PS 0	19	19	
PS 1	20	20	
PS 2	7	7	
Brain result Units: Subjects			
Abnormal	14	14	
Normal	32	32	
PD-L1 Units: Subjects			
Negative	26	26	
Positive (>= 1 and < 50%)	16	16	
Positive (>= 50%)	3	3	
Unknown	1	1	
HER2 results Units: Subjects			
in-frame insertions in exon 20	32	32	
point mutations L755S and G776C	2	2	
other mutation/insertion	12	12	
EGFR results Units: Subjects			
Indeterminate	1	1	
Wild-type (wt)	44	44	
Not done	1	1	
ALK results Units: Subjects			
Wild-type (wt)	45	45	
Not done	1	1	
ROS1 results Units: Subjects			
Wild-type (wt)	42	42	
Not done	4	4	
PI3K results Units: Subjects			
Negative	22	22	
Not done	24	24	
KRAS results Units: Subjects			
Indeterminate	1	1	
Negative	42	42	
Not done	3	3	
BRAF results			

Units: Subjects			
Indeterminate	1	1	
Negative	42	42	
Not done	3	3	
Number of pack year			
Units: Pack year			
median	14.0		
full range (min-max)	3 to 40	-	

End points

End points reporting groups

Reporting group title	Pertuzumab - Trastuzumab - Docetaxel

Reporting group description:

Pertuzumab was administered as an intravenous (IV) loading dose of 840 mg once every 3 weeks on day 1 of cycle 1 (1 cycle length 5 21 days), and 420 mg once every 3 weeks on day 1 of subsequent cycles. Trastuzumab was
administered as an IV loading dose of 8 milligrams per kilogram (mg/kg) once every 3 weeks on day 2 of cycle 1 (1 cycle length 5 21 days), and 6 mg/kg once every 3 weeks on day 1 of subsequent cycles. Docetaxel was administered as an IV dose of 75 milligrams per square meter of body surface area (mg/m2) once every 3 weeks on day 2 of cycle 1 (1 cycle length 5 21 days), and 75 mg/m2 once every 3 weeks on day 1 of subsequent cycles. Treatment was given until toxicity or disease progression.

Primary: Confirmed Overall Response Rate (ORR) at 6 weeks

End point title	Confirmed Overall Response Rate (ORR) at 6 weeks[1]

End point description:

ORR is defined as the proportion of patients with a confirmed complete response or partial response at 6 weeks (confirmed at least after 4 weeks) according to RECIST version 1.1.

End point type	Primary

End point timeframe:

6 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not applicable as the study was single arm.

End point values	Pertuzumab - Trastuzumab - Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: % of participants				
median (confidence interval 95%)	13.3 (3.4 to 23.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR is defined as the proportion of patients with a confirmed complete response or partial response according to RECIST version 1.1.

End point type	Secondary

End point timeframe:

Median follow-up of 12 months (95% CI, 6.7 to 14.4)

End point values	Pertuzumab - Trastuzumab - Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: % of participants				
median (confidence interval 95%)	28.9 (15.6 to 42.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression-free survival is defined as the time from enrollment to first observation of progression (according to RECIST v1.1) or date of death (from any cause).

End point type	Secondary

End point timeframe:

Median follow-up of 12 months (95% CI, 6.7 to 14.4)

End point values	Pertuzumab - Trastuzumab - Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Months				
median (confidence interval 95%)	6.83 (4.0 to 8.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of response is defined as the time from documentation of tumor response to disease progression.

End point type	Secondary

End point timeframe:

Median follow-up of 12 months (95% CI, 6.7 to 14.4)

End point values	Pertuzumab - Trastuzumab - Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Months				
median (confidence interval 95%)	5.6 (2.7 to 14.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival, defined as the time from enrollment until death due to any cause, will be the principal secondary endpoint.

End point type	Secondary

End point timeframe:

Median follow-up of 12 months (95% CI, 6.7 to 14.4)

End point values	Pertuzumab - Trastuzumab - Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: % of participants				
median (confidence interval 95%)	17.6 (11.6 to 18.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for collection of adverse events extended from the date of signature of the informed consent until 30 days after the last day of study treatment.

Adverse event reporting additional description:

The maximal grade of adverse events was collected by cycle of treatment and during follow-up.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Treated

Reporting group description: -

Serious adverse events	Treated		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 45 (48.89%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression	Additional description: Neoplasm progression		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Vascular disorders			
Superior vena cava syndrome	Additional description: Superior vena cava syndrome		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death	Additional description: Sudden death		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Craniocerebral injury	Additional description: Craniocerebral injury		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture	Additional description: Femur fracture		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Overdose	Additional description: Overdose		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion	Additional description: Pericardial effusion		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial	Additional description: Haemorrhage intracranial		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage	Additional description: Upper gastrointestinal haemorrhage		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism	Additional description: Hyperthyroidism		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection	Additional description: Device related infection		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung infection	Additional description: Lung infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii pneumonia	Additional description: Pneumocystis jirovecii pneumonia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural infection	Additional description: Pleural infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Treated		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)		
Vascular disorders			
Embolism	Additional description: Embolism		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Hot flush	Additional description: Hot flush		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypertension	Additional description: Hypertension		
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	17		
Phlebitis	Additional description: Phlebitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	12		
General disorders and administration site conditions			
Face oedema	Additional description: Face oedema		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	5		
Fatigue	Additional description: Fatigue		
subjects affected / exposed	37 / 45 (82.22%)		
occurrences (all)	224		
Influenza like illness	Additional description: Influenza like illness		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Malaise	Additional description: Malaise		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Localised oedema	Additional description: Localised oedema		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	11		
Pain	Additional description: Pain		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	15		
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	30		
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	8		
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylactic reaction		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Pelvic pain	Additional description: Pelvic pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	6		
Vulvovaginal inflammation	Additional description: Vulvovaginal inflammation		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	Additional description: Acute respiratory distress syndrome		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Cough	Additional description: Cough		

subjects affected / exposed	13 / 45 (28.89%)		
occurrences (all)	36		
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	14 / 45 (31.11%)		
occurrences (all)	80		
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	10 / 45 (22.22%)		
occurrences (all)	26		
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Productive cough	Additional description: Productive cough		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	16		
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Rhinitis allergic	Additional description: Rhinitis allergic		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	5		
Rhinorrhoea	Additional description: Rhinorrhoea		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	11		
Confusional state	Additional description: Confusional state		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	5		
Depression	Additional description: Depression		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	6		
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		

Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	21		
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	12		
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	23		
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	9		
Ejection fraction decreased	Additional description: Ejection fraction decreased		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	26		
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	9		
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	17 / 45 (37.78%)		
occurrences (all)	32		
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	11 / 45 (24.44%)		
occurrences (all)	53		
Injury, poisoning and procedural complications			

Fracture	Additional description: Fracture		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vascular access complication	Additional description: Vascular access complication		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Cardiac disorders			
Sinus tachycardia	Additional description: Sinus tachycardia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	3		
Ventricular hypokinesia	Additional description: Ventricular hypokinesia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia	Additional description: Amnesia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	5		
Aphasia	Additional description: Aphasia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	3		
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	37		
Encephalopathy	Additional description: Encephalopathy		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	6		
Dysarthria	Additional description: Dysarthria		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Headache	Additional description: Headache		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	7		
Memory impairment	Additional description: Memory impairment		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	8		
Myasthenia gravis	Additional description: Myasthenia gravis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Peripheral motor neuropathy	Additional description: Peripheral motor neuropathy		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	5		
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	10 / 45 (22.22%)		
occurrences (all)	45		
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
subjects affected / exposed	14 / 45 (31.11%)		
occurrences (all)	55		
Pyramidal tract syndrome	Additional description: Pyramidal tract syndrome		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	4		
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Tremor	Additional description: Tremor		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	25 / 45 (55.56%)		
occurrences (all)	115		
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain	Additional description: Ear pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vertigo	Additional description: Vertigo		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	5		
Eye disorders			
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	41		
Dry eye	Additional description: Dry eye		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	14		
Diplopia	Additional description: Diplopia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	4		
Lacrimation increased	Additional description: Lacrimation increased		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	21		
Periorbital oedema	Additional description: Periorbital oedema		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	13		
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	10		
Anal haemorrhage	Additional description: Anal haemorrhage		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	9		
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Colitis	Additional description: Colitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Constipation	Additional description: Constipation		

subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	23		
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	32 / 45 (71.11%)		
occurrences (all)	125		
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	5		
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	5		
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	14		
Gastrointestinal pain	Additional description: Gastrointestinal pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	3		
Gastritis	Additional description: Gastritis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Nausea	Additional description: Nausea		
subjects affected / exposed	19 / 45 (42.22%)		
occurrences (all)	43		
Oral pain	Additional description: Oral pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Rectal haemorrhage	Additional description: Rectal haemorrhage		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Toothache	Additional description: Toothache		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Stomatitis	Additional description: Stomatitis		

subjects affected / exposed	14 / 45 (31.11%)		
occurrences (all)	41		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	11 / 45 (24.44%)		
occurrences (all)	20		
Hepatobiliary disorders			
Hepatic pain	Additional description: Hepatic pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	22 / 45 (48.89%)		
occurrences (all)	123		
Dry skin	Additional description: Dry skin		
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	17		
Dermatitis acneiform	Additional description: Dermatitis acneiform		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	7		
Eczema	Additional description: Eczema		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Erythema multiforme	Additional description: Erythema multiforme		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	17		
Nail discolouration	Additional description: Nail discolouration		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	13		
Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	23		
Onychomadesis	Additional description: Onychomadesis		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	16		
Onycholysis	Additional description: Onycholysis		

subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	14		
Pain of skin	Additional description: Pain of skin		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	3		
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Palmar-plantar erythrodysaesthesia syndrome		
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	14		
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	5		
Pruritus	Additional description: Pruritus		
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	34		
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	16		
Rash	Additional description: Rash		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Skin fissures	Additional description: Skin fissures		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	10		
Skin reaction	Additional description: Skin reaction		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Urticaria	Additional description: Urticaria		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Chronic kidney disease	Additional description: Chronic kidney disease		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	10		
Cystitis noninfective	Additional description: Cystitis noninfective		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	5		
Dysuria	Additional description: Dysuria		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	6		
Renal failure	Additional description: Renal failure		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Urinary retention	Additional description: Urinary retention		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	8		
Endocrine disorders			
Hyperparathyroidism	Additional description: Hyperparathyroidism		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	6		
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	6		
Thyroiditis	Additional description: Thyroiditis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis	Additional description: Arthritis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	20		
Back pain	Additional description: Back pain		

subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	13		
Bone pain	Additional description: Bone pain		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	9		
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	5		
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	9		
Myalgia	Additional description: Myalgia		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Neck pain	Additional description: Neck pain		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	5		
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Corona virus infection	Additional description: Corona virus infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Device related infection	Additional description: Device related infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Fungal infection	Additional description: Fungal infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

Folliculitis	Additional description: Folliculitis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nail infection	Additional description: Nail infection		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	18		
Paronychia	Additional description: Paronychia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	5		
Rash pustular	Additional description: Rash pustular		
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	12		
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Skin infection	Additional description: Skin infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	14		
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	13		

Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	31		
Hypomagnesaemia	Additional description: Hypomagnesaemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Hypoalbuminaemia	Additional description: Hypoalbuminaemia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	4		
Hypercalcaemia	Additional description: Hypercalcaemia		
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2019	A substantial modification was done in order to: - clarify main objective and update secondary objectives - clarify some inclusion criteria : possibilty to include patients with HER mutations not listed upon IFCT approval ; possibilty to include patients with history of haematological toxicity grade 2 if previous treatment with taxanes, delete the type of exam required for the evaluation of LVEF, update of criteria about contraception - add a maximum of 14 days between enrolment and start of treatment - clarify surveillance period after infusion of pertuzumab and trastuzumab including the repetition of the loading dose if the delay between 2 injections exceeds 6 weeks. - add the managment of toxicity in case LVEF <50%
05 August 2020	A substantial modification was done in order to: - change main objective, secondary objectives and exploratory objectives - delete the interim analysis - addition of a blood sample at progression and the possibility of rebiopsy at progression
25 January 2021	A substantial modification was done in order to: - homogenize study design according the sample size assumptions - correct the main objective according to the analysis of the primary endpoint - correct statistical section after the deletion of the interim analysis
22 December 2021	A substantial modification was done in order to increase the duration of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35073148