



## Clinical trial results:

### A Phase II Trial Evaluating the Combined Use of Gemcitabine, Trastuzumab and Erlotinib as a First Line Chemotherapy Treatment in Patients with Metastatic Adenocarcinoma of the Pancreas

#### Summary

EudraCT number	2009-016875-30
Trial protocol	FR
Global end of trial date	19 January 2016

#### Results information

Result version number	v1 (current)
This version publication date	23 February 2023
First version publication date	23 February 2023

#### Trial information

##### Trial identification

Sponsor protocol code	VA 2009/40
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01204372
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	INSTITUT DU CANCER DE MONTPELLIER (ICM)
Sponsor organisation address	208 RUE DES APOTHICAIRES, MONTPELLIER, France, 34298 CEDEX 5
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Scientific contact	Aurore MOUSSION, INSTITUT DU CANCER DE MONTPELLIER, 33 0467613102, Drci-icm105@icm.unicancer.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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	12 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2014
Global end of trial reached?	Yes
Global end of trial date	19 January 2016
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

Evaluate the rate of disease control according to the criteria RECIST from the combined use of gemcitabine, trastuzumab and erlotinib.

Protection of trial subjects:

In order to ensure the safety protection of trial subjects, G-CSF had been added

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	France: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

Notes:

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**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)	46
From 65 to 84 years	17
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

- Metastatic adenocarcinoma of the pancreas confirmed by histology available
- Lesion able to be measured according to the criteria RECIST
- Index of performance  $\leq 1$  according to OMS
- Age of patient  $\geq 18$  y/old
- Life expectancy of at least 3 months

### Period 1

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

### Arms

Arm title	SINGLE ARM
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Arm description:

GEMCITABINE + TRASTUZUMAB + ERLOTINIB

Arm type	Experimental
Investigational medicinal product name	GEMCITABINE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intraventricular use

Dosage and administration details:

DOSAGE : 1000 mg/m<sup>2</sup>

For the first eight weeks of treatment the injections will be given at D1, D8, D15, D22, D29, D36 and D43 followed by one week of rest (one injection/week, 7 weeks/8). Subsequently, gemcitabine will be administered at D1, D8 and D15 of each 4 week cycle (one injection/week, 3 weeks/4).

Investigational medicinal product name	TRASTUZUMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intraventricular use

Dosage and administration details:

DOSAGE : 4 mg/kg

Every week :. It will be administered at a dose of 4 mg/kg over 90 minutes at D1 and then at 2 mg/kg over 30 minutes for the subsequent perfusions.

Investigational medicinal product name	ERLOTINIB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

The erlotinib will be administered orally at a dose of 100mg/day from C1D1.

<b>Number of subjects in period 1</b>	SINGLE ARM
Started	63
Completed	63

## Baseline characteristics

### Reporting groups

Reporting group title	OVERALL TRIAL
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Reporting group description: -

Reporting group values	OVERALL TRIAL	Total	
Number of subjects	63	63	
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)	46	46	
From 65-84 years	17	17	
85 years and over	0	0	
18-64	0	0	
Age continuous			
Units: years			
median	62		
full range (min-max)	35 to 77	-	
Gender categorical			
Units: Subjects			
Female	26	26	
Male	37	37	

### Subject analysis sets

Subject analysis set title	PER PROTOCOL
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Subject analysis set type	Per protocol
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Subject analysis set description:

All included patients in the study and who received at least one treatment administration with no major violation of the inclusion or non-inclusion criteria.

Subject analysis set title	Efficacy population
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

All included patients in the study who completed at least 2 cycles of treatment or discontinued for tumor progression

Reporting group values	PER PROTOCOL	Efficacy population	
Number of subjects	62	59	
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)	45	44	
From 65-84 years	17	15	
85 years and over	0	0	
18-64	0	0	
Age continuous			
Units: years			
median	62	62	
full range (min-max)	35 to 77	35 to 77	
Gender categorical			
Units: Subjects			
Female			
Male			

## End points

### End points reporting groups

Reporting group title	SINGLE ARM
Reporting group description: GEMCITABINE + TRASTUZUMAB + ERLOTINIB	
Subject analysis set title	PER PROTOCOL
Subject analysis set type	Per protocol
Subject analysis set description: All included patients in the study and who received at least one treatment administration with no major violation of the inclusion or non-inclusion criteria.	
Subject analysis set title	Efficacy population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All included patients in the study who completed at least 2 cycles of treatment or discontinued for tumor progression	

### Primary: DISEASE CONTROL

End point title	DISEASE CONTROL <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe: Every 8 weeks and at the treatment completion	

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: With a one-stage Fleming design, under the hypotheses  $\alpha = 5\%$ ,  $\beta = 7.5\%$ ,  $p_0$  (the maximum inefficiency probability) = 40% and  $p_1$  (the minimum efficiency probability) = 60%, it is necessary to include 57 evaluable patients.

If we consider only the first 57 evaluable patients, we observe a stabilization of the disease in 42/57 patients. According to the decision rule defined in the protocol, we therefore conclude that the trial is positive for the main endpoint.

End point values	SINGLE ARM	Efficacy population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	59		
Units: PATIENT				
YES	44	44		
NO	15	15		

Attachments (see zip file)	3-STAT_Rapport_GATE1_2014_07_17.pdf
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### Statistical analyses

No statistical analyses for this end point

### Secondary: PROGRESSION FREE SURVIVAL

End point title	PROGRESSION FREE SURVIVAL
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End point description:

PROGRESSION FREE RATE AT 6 MONTHS

End point type	Secondary
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End point timeframe:

Every 8 weeks and at the treatment completion

End point values	PER PROTOCOL			
Subject group type	Subject analysis set			
Number of subjects analysed	62			
Units: percent				
number (confidence interval 95%)	25.8 (15.7 to 37.1)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: OVERALL SURVIVAL

End point title	OVERALL SURVIVAL
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End point description:

OVERALL SURVIVAL RATE AT 6 MONTHS

End point type	Secondary
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End point timeframe:

Every 8 weeks and at the treatment completion

End point values	PER PROTOCOL			
Subject group type	Subject analysis set			
Number of subjects analysed	62			
Units: percent				
number (confidence interval 95%)	56.5 (43.2 to 67.7)			

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

EVERY 4 WEEKS

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI-CTCAE
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Dictionary version	3.0
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### Reporting groups

Reporting group title	SAFETY POPULATION
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Reporting group description:

ALL INCLUDED PATIENTS AND WHO RECEIVED AT LEAST ONE DOSE OF TREATMENT

Serious adverse events	SAFETY POPULATION		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 62 (41.94%)		
number of deaths (all causes)	27		
number of deaths resulting from adverse events	12		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Vascular disorders			
Oedema			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
cardiogenic shoc			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
CARDIO RESPIRATORY ARREST			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic thrombosis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Abdominal Pain			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 7		
Embolism			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 4		
Cerebrovascular accident			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
fever			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
diabetes			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
anorexia			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Death			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Vertigo			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MUCOSITIS			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
ACCIDENTAL STUDY DRUG OVERDOSING			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences causally related to treatment / all	4 / 9		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	3 / 62 (4.84%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
OCCLUSION			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nausea			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 1		
Ileus			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal stenosis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
small intestine occlusion			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
HEMATEMESIS			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Cholecystitis			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ascites			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plexus alcoolisation			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary tract infection			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bile duct stenosis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Hiccups			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
infectious pneumopathy			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	SAFETY POPULATION		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 62 (100.00%)		
Vascular disorders			
Phlebitis			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
General disorders and administration site conditions			
Dysgeusia			
subjects affected / exposed	25 / 62 (40.32%)		
occurrences (all)	25		
Dyspepsia			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Dysphagia			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Weight decreased			
subjects affected / exposed	32 / 62 (51.61%)		
occurrences (all)	32		
Oedema			
subjects affected / exposed	25 / 62 (40.32%)		
occurrences (all)	25		
Asthenia			
subjects affected / exposed	57 / 62 (91.94%)		
occurrences (all)	57		
fever			

subjects affected / exposed	25 / 62 (40.32%)		
occurrences (all)	25		
General physical health deterioration			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	10		
Arthralgia			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Epistaxis			
subjects affected / exposed	22 / 62 (35.48%)		
occurrences (all)	22		
Chills			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	13		
sweating			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Immune system disorders			
allergy			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
Throat irritation			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Dysphonia			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	7		
Dyspnoea			
subjects affected / exposed	18 / 62 (29.03%)		
occurrences (all)	18		
pneumopathy			

subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5		
Rhinitis subjects affected / exposed occurrences (all)	16 / 62 (25.81%) 16		
Cough subjects affected / exposed occurrences (all)	13 / 62 (20.97%) 13		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	9 / 62 (14.52%) 9		
Insomnia subjects affected / exposed occurrences (all)	16 / 62 (25.81%) 16		
Depression subjects affected / exposed occurrences (all)	9 / 62 (14.52%) 9		
Cardiac disorders Thrombosis subjects affected / exposed occurrences (all)	27 / 62 (43.55%) 27		
Ejection fraction decreased subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4		
Hypertension subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3		
Nervous system disorders Neurological symptom subjects affected / exposed occurrences (all)	19 / 62 (30.65%) 19		
Headache subjects affected / exposed occurrences (all)	6 / 62 (9.68%) 6		
Tremor			



subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Vertigo			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	61 / 62 (98.39%)		
occurrences (all)	61		
Neutropenia			
subjects affected / exposed	42 / 62 (67.74%)		
occurrences (all)	42		
thrombopenia			
subjects affected / exposed	44 / 62 (70.97%)		
occurrences (all)	44		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	48 / 62 (77.42%)		
occurrences (all)	48		
Constipation			
subjects affected / exposed	39 / 62 (62.90%)		
occurrences (all)	39		
Abdominal pain			
subjects affected / exposed	57 / 62 (91.94%)		
occurrences (all)	57		
Nausea			
subjects affected / exposed	45 / 62 (72.58%)		
occurrences (all)	45		
Vomiting			
subjects affected / exposed	35 / 62 (56.45%)		
occurrences (all)	35		
Stomatitis			
subjects affected / exposed	37 / 62 (59.68%)		
occurrences (all)	37		
bloating			

subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		
Epigastric discomfort			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	13		
Flatulence			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
Haemorrhoids			
subjects affected / exposed	12 / 62 (19.35%)		
occurrences (all)	12		
Hiccups			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
meteorism			
subjects affected / exposed	9 / 62 (14.52%)		
occurrences (all)	9		
buccal mycosis			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
occlusion			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
gastroesophageal reflux			
subjects affected / exposed	21 / 62 (33.87%)		
occurrences (all)	21		
Dry mouth			
subjects affected / exposed	11 / 62 (17.74%)		
occurrences (all)	11		
Ascites			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
Hepatobiliary disorders			

Hyperbilirubinaemia subjects affected / exposed occurrences (all)	7 / 62 (11.29%) 7		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	54 / 62 (87.10%) 54		
Paronychia subjects affected / exposed occurrences (all)	8 / 62 (12.90%) 8		
hand fissure subjects affected / exposed occurrences (all)	8 / 62 (12.90%) 8		
Cheilitis subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5		
Pruritus subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4		
Dry skin subjects affected / exposed occurrences (all)	14 / 62 (22.58%) 14		
Alopecia subjects affected / exposed occurrences (all)	11 / 62 (17.74%) 11		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5		
Musculoskeletal and connective tissue disorders			
muscle cramp subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3		
costal pain subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3		

Back pain			
subjects affected / exposed	13 / 62 (20.97%)		
occurrences (all)	13		
shoulder pain			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
lumbar pain			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	7		
legs pain			
subjects affected / exposed	8 / 62 (12.90%)		
occurrences (all)	8		
arm pain			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
thoracic pain			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
Infections and infestations			
Infection			
subjects affected / exposed	27 / 62 (43.55%)		
occurrences (all)	27		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	10		
Anorexia and bulimia syndrome			
subjects affected / exposed	55 / 62 (88.71%)		
occurrences (all)	55		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2011	PROTOCOL MODIFICATION: toxicities management & MODIFICATION OF INVESTIGATOR LISTING
28 January 2013	PROTOCOL MODIFICATIONS : Pharmacovigilance process updated & MODIFICATIONS OF INVESTIGATORS LISTING
27 May 2013	PROTOCOL MODIFICATIONS : Modification of study period & MODIFICATIONS OF INVESTIGATORS LISTING
18 March 2014	PROTOCOL MODIFICATIONS : Trastuzumab BI updated & Modification of consent following Trastuzumab BI changes

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Adverse Events (AE) section: occurrence of each AE was not available, we fulfilled with the number of patients.

Notes:

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33405269>