Clinical trial results:
A phase III trial of vinflunine + capecitabine versus capecitabine alone in patients with advanced breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant

Summary

EudraCT number	2008-004171-21
Trial protocol	ES FR CZ EE IT GB BE HU BG
Global end of trial date	18 February 2015

Results information

Result version number	v1
This version publication date	09 June 2016
First version publication date	09 June 2016

Trial information

Trial identification

Sponsor protocol code	L00070 IN 3 05 B0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01095003
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Medicament
Sponsor organisation address	45 Place Abel Gance, Boulogne Billancourt, France, 92654
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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	15 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2011
Global end of trial reached?	Yes
Global end of trial date	18 February 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study investigated the comparative efficacy (progression free survival (primary criteria), response to treatment and disease control parameters (secondary criteria)) of vinflunine plus capecitabine versus capecitabine alone in patients with metastatic breast cancer who were previously treated with or resistant to an anthracycline and who were taxane resistant.

Protection of trial subjects:

The trial was conducted according to Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki and its subsequent amendments thereto and local legal regulations. The study protocol and the informed consent form were submitted for approval to Ethics Committees before the study set up according to the national regulations. The patient underwent a health assessment at the start of the study and remained under regular medical control during the whole study.

Background therapy:

Antiemetic prophylaxis (dexamethasone 8mg or equivalent just before each infusion) and constipation prophylaxis (ditary measures and laxatives from day1 to 5 of each cycle)

Evidence for comparator: -

Actual start date of recruitment	06 May 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	France: 100
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Belarus: 84
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	India: 101
Country: Number of subjects enrolled	Mexico: 12

Country: Number of subjects enrolled	Serbia: 7
Country: Number of subjects enrolled	South Africa: 21
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Ukraine: 117
Country: Number of subjects enrolled	Argentina: 22
Country: Number of subjects enrolled	Russian Federation: 103
Worldwide total number of subjects	770
EEA total number of subjects	274

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)	669
From 65 to 84 years	101
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 6th of May 2009 (First patient enrolled) up to 25th May 2011 (last patient enrolled), 770 patients were enrolled from 129 active centres in 21 countries. Patients were to be treated until disease progression, unacceptable toxicity or patient's request. After the study treatment discontinuation, patients were to be followed until death.

Pre-assignment

Screening details:

-21 years and older female patients, with an histologically/cytologically confirmed breast carcinoma, documented locally recurrent or metastatic disease not amenable to curative surgery or radiotherapy
-Having received at least one prior chemotherapy (neo/adjuvant setting)
-previously treated with or resistant to anthracycline and taxane

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Capecitabine single agent

Arm description: -

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

Dosage and administration details:

Patients received: Capecitabine at the dose of 1250 mg/m² per os twice per day each morning and each evening for 14 consecutive days beginning on day 1 of each cycle repeated every 3 weeks (self-administered).

Arm title	Vinflunine + capecitabine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received:
Capecitabine at the dose of 825mg/m² per os twice per day each morning and each evening for 14 consecutive days beginning on day 1 of each cycle repeated every 3 weeks (self-administered).

Investigational medicinal product name	Vinflunine
Investigational medicinal product code	L00070 IN
Other name	Javlor
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients received (in combination with capecitabine)
• Vinflunine at the dose of 280 mg/m² and as a 20-minute IV. infusion on day 1 of each cycle repeated every 3 weeks.

Number of subjects in period 1	Capecitabine single agent	Vinflunine + capecitabine
Started	386	384
cut-off date: 20 december 2011	144	143
cut-off date: 15 March 2013	60	49
Completed	60	49
Not completed	326	335
death	319	324
Lost to follow-up	7	11

Baseline characteristics

Reporting groups	
Reporting group title	Capecitabine single agent
Reporting group description: -	
Reporting group title	Vinflunine + capecitabine
Reporting group description: -	

Reporting group values	Capecitabine single agent	Vinflunine + capecitabine	Total
Number of subjects	386	384	770
Age categorical Units: Subjects			
Adults (18-64 years)	340	329	669
From 65-84 years	46	55	101
85 years and over	0	0	0
Age continuous Units: years			
median	54	53.6	
full range (min-max)	26.8 to 77.7	27 to 80.6	-
Gender categorical Units: Subjects			
Female	386	384	770
Male	0	0	0
Karnofski Performance status			
Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment The lower the Karnofsky score, the worse the survival for most serious illnesses: The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is death.			
Units: Subjects			
90-100	247	253	500
70-80	138	130	268
<70	1	1	2
Main histopathological type of breast cancer Units: Subjects			
ductal	273	283	556
lobular	40	29	69
carcinoma NOS	54	43	97
others	19	29	48
Desease measurability Units: Subjects			
Yes	343	339	682
No	43	45	88
Time from diagnosis Units: years			
median	2.1	2.4	
full range (min-max)	0.2 to 31.5	0.2 to 21.2	-

End points

End points reporting groups

Reporting group title	Capecitabine single agent
Reporting group description: -	
Reporting group title	Vinflunine + capecitabine
Reporting group description: -	

Primary: Progression Free survival (PFS)

End point title	Progression Free survival (PFS)

End point description:

PFS is defined as time from date of randomization to date of the first documentation of objective tumor progression (according to the IRC and based on RECIST version 1.1) or death due to any cause
The PFS was primarily analysed in the Intent-to-treat (ITT) population. Patients lost to follow-up, or without a known record of progression or death at time of analysis had the progression-free survival censored at the date of last tumour assessment or the date of last contact of a follow-up showing no progression, whichever occurs last.

End point type	Primary

End point timeframe:

Baseline up to first cut-off date (20 december 2011)

End point values	Capecitabine single agent	Vinflunine + capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386[1]	384[2]		
Units: Months				
median (confidence interval 95%)	4.3 (4.1 to 5.6)	5.6 (5.3 to 6.3)		

Notes:

[1] - 312 events -74 censored patients

[2] - 312 events- 70 censored

Statistical analyses

Statistical analysis title	Primary efficacy analysis

Statistical analysis description:

The final analysis of progression free survival was conducted once the required number of events(615 progressions or deaths) was reached.
using the IRC assessment of date of progressions following the blinded radiological and clinical review of data. Kaplan-Meier curves and life tables by treatment arm were provided.
A stratified Cox proportional model was used to compare the two treatment arms tak

Comparison groups	Capecitabine single agent v Vinflunine + capecitabine
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0426 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.99

Notes:

[3] - The primary efficacy analysis of the PFS was performed in the intent-to-treat (ITT) population

[4] - According to the IRC, the median PFS was of 5.6 months for the VFL+CAPE arm and 4.3 months for the CAPE single agent arm and the difference was statistically significant (HR= 0.84, 95%CI 0.71-0.99; P=0.0426)

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

The overall survival (OS) was defined as the duration between the date of randomisation and the date of death from any cause. The OS analysis was performed in the ITT population and the eligible and perprotocol populations once the required number of events (631 deaths) was observed
Patients lost to follow-up, or without a known record of death at time of analysis had the OS censored at the date of last contact.

End point type	Secondary

End point timeframe:

Baseline up to the cut-off date set on 15 March, 2013 (final analysis). At the cut-off date 83.5% of all patients had progressed or died (death as first event)

End point values	Capecitabine single agent	Vinflunine + capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386[5]	384[6]		
Units: Months				
median (confidence interval 95%)	11.7 (10.8 to 13.5)	13.9 (11.9 to 15)		

Notes:

[5] - 319 events-67 censored

[6] - 324 events 60 censored

Statistical analyses

Statistical analysis title	Overall survival analysis

Statistical analysis description:

OS is defined as time from date of randomization to date of death due to any cause The final analysis of survival was conducted in the ITT population after 643 deaths have been observed (83.5% of all patients, 84.4% in the VFL+CAPE arm and 82.6% in the CAPE arm respectively).

Comparison groups	Capecitabine single agent v Vinflunine + capecitabine
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.7657 [8]
Method	stratified Log rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.15

Notes:

[7] - To describe time dependent parameters, Kaplan-Meier curves and life tables by treatment arm are provided. Confidence intervals on the median were calculated using the Brookmeyer and Crowley method. Hazard ratio and 95% confidence intervals are reported. A stratified Cox proportional model was performed to compare the two treatment arms taking into account the stratification factors (except centre) used at the time of randomisation.
[8] - The IRC assessed ORR was higher in the VFL+CAPE arm compared to the CAPE arm in ITT (and in all studied populations) even though this difference (+2.2 months) did not reach statistical significance.

Secondary: Overall Response rate (ORR=CR+PR)

End point title	Overall Response rate (ORR=CR+PR)

End point description:

ORR defined as documentation of complete or partial response that was subsequently confirmed to first documentation of disease progression or to death due to any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

From baseline to 1st cut-off date

End point values	Capecitabine single agent	Vinflunine + capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386	384		
Units: percent				
median (confidence interval 95%)	17.9 (14.2 to 22.1)	22.9 (18.8 to 27.5)		

Statistical analyses

Statistical analysis title	Overall response rate at 1st cut off date

Statistical analysis description:

The analyses of tumour response were performed in the ITT population and in the population evaluable for response in the two treatment. Tumour response rate (overall response rate, ORR) defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) as best overall (across all time points) response from the date of randomisation until disease progression but within 30 days from the last administration.

Comparison groups	Capecitabine single agent v Vinflunine + capecitabine
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.103 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Median difference (final values)

Notes:

[9] - The overall response rate (ORR) was first evaluated according to IRC and compared between the two arms with a Cochran-Mantel-Haenszel test stratified on the stratification factors at randomisation (except centre). Furthermore, the ORR was estimated

[10] - ORR was higher in the VFL+CAPE arm compared to the CAPE arm in all studied populations even though this difference did not reach statistical significance

Secondary: Disease Control rate

End point title	Disease Control rate

End point description:

Disease control rate defined (DCR) as the proportion of patients who achieved at least a stabilisation of the disease not counting patients with only non-measurable disease at baseline and best overall response of non-CR/non-PD.

End point type	Secondary

End point timeframe:

from Baseline to first cut-off date

End point values	Capecitabine single agent	Vinflunine + capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386	384		
Units: percent				
median (confidence interval 95%)	47.9 (42.9 to 53)	57.3 (52.2 to 62.3)		

Statistical analyses

Statistical analysis title	disease control rate analysis

Statistical analysis description:

Disease control rate defined (DCR) as the proportion of patients who achieved at least a stabilisation of the disease not counting patients with only non-measurable
disease at baseline and best overall response of non-CR/non-PD.

Comparison groups	Capecitabine single agent v Vinflunine + capecitabine
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0089 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Median difference (final values)

Notes:

[11] - The 95% confidence interval for proportions was computed following the exact method. Stratified analyses were performed using a Cochran-Mantel-Haenszel

[12] - The DCR as per IRC in the ITT population was significantly increased (+9.4%; p=0.0089) in the VFL+CAPE arm compared to the CAPE arm (57.3% and 47.9% respectively)

Secondary: Duration of response

End point title	Duration of response

End point description:

Measured from the first time that measurement criteria were first met for objective response (documented CR or PR) until recurrence/progression or death whatever the cause.

End point type	Secondary

End point timeframe:

from Baseline to cut-off date

End point values	Capecitabine single agent	Vinflunine + capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386	384		
Units: Months				
median (confidence interval 95%)	5.5 (4.1 to 6.9)	8.4 (4.9 to 9.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs are reported from time of first dose of study treatment up to 30 days after last dose of study treatment at the exceptions of SAEs occurring after discontinuation and start of a further treatment

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as nonserious in another. Specific AE tables were generated separately as per EU format. We report here all on study SAEs and only Treatment related AEs by SOC and PT (PT>=1%)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Capecitabine single agent

Reporting group description:

Overall 90.1% of "all treated Capecitabine patients" (N=383) experienced at least one AE and 73.6% at least one related AE. 21.7% experienced at least one SAE of which 6% were treatment related
Among them we will detail and report AEs related to treatment (PT >=1%) and all SAEs experienced during the treatment period whatever the Relationship with treatment

Reporting group title	Vinflunine + capecitabine

Reporting group description:

Overall 94% of "all treated Vinflunine + Capecitabine patients" (N=383) experienced at least one AE and 79.6% at least one related AE. 26.9% experienced at least one SAE of which 13.3% were treatment related.
We report here AEs related to treatment (PT >=1%) and all SAEs experienced during the treatment period whatever the Relationship with treatment

Serious adverse events	Capecitabine single agent	Vinflunine + capecitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 383 (21.67%)	103 / 383 (26.89%)	
number of deaths (all causes)	235	232	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	31 / 383 (8.09%)	34 / 383 (8.88%)	
occurrences causally related to treatment / all	0 / 34	0 / 34	
deaths causally related to treatment / all	0 / 18	0 / 20	
Malignant pleural effusion			
subjects affected / exposed	0 / 383 (0.00%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cancer pain			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 383 (0.26%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	0 / 383 (0.00%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anal fistula excision			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stent insertion			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoid operation			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 383 (0.26%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related complication			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 383 (0.52%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Condition aggravated			
subjects affected / exposed	6 / 383 (1.57%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	2 / 7	1 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	

Death			
subjects affected / exposed	2 / 383 (0.52%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	0 / 383 (0.00%)	3 / 383 (0.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (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			
Pulmonary embolism			
subjects affected / exposed	3 / 383 (0.78%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 383 (1.31%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Biopsy			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			

subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 383 (0.52%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Brachial plexopathy			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 383 (0.78%)	4 / 383 (1.04%)	
occurrences causally related to treatment / all	3 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 383 (0.52%)	7 / 383 (1.83%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	2 / 2	
Neutropenia			
subjects affected / exposed	1 / 383 (0.26%)	6 / 383 (1.57%)	
occurrences causally related to treatment / all	1 / 1	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 383 (0.26%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 383 (0.00%)	8 / 383 (2.09%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intestinal obstruction			
subjects affected / exposed	1 / 383 (0.26%)	6 / 383 (1.57%)	
occurrences causally related to treatment / all	0 / 3	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 383 (0.26%)	4 / 383 (1.04%)	
occurrences causally related to treatment / all	1 / 1	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 383 (0.00%)	6 / 383 (1.57%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 383 (0.78%)	5 / 383 (1.31%)	
occurrences causally related to treatment / all	1 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 383 (1.57%)	4 / 383 (1.04%)	
occurrences causally related to treatment / all	6 / 8	5 / 5	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 383 (0.26%)	3 / 383 (0.78%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 383 (0.00%)	3 / 383 (0.78%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux gastritis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	3 / 383 (0.78%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	2 / 383 (0.52%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
musculoskeletal chest pain			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 383 (0.52%)	3 / 383 (0.78%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower respiratory tract infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 383 (0.26%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia			
subjects affected / exposed	1 / 383 (0.26%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 383 (0.00%)	2 / 383 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 383 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 383 (0.26%)	0 / 383 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Capecitabine single agent	Vinflunine + capecitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	262 / 383 (68.41%)	257 / 383 (67.10%)	
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 383 (0.00%)	4 / 383 (1.04%)	
occurrences (all)	0	4	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	47 / 383 (12.27%)	71 / 383 (18.54%)	
occurrences (all)	86	145	
Asthenia			
subjects affected / exposed	30 / 383 (7.83%)	58 / 383 (15.14%)	
occurrences (all)	41	162	
Injection site reaction			
subjects affected / exposed	0 / 383 (0.00%)	55 / 383 (14.36%)	
occurrences (all)	0	153	
Pyrexia			
subjects affected / exposed	7 / 383 (1.83%)	21 / 383 (5.48%)	
occurrences (all)	7	42	
Pain			
subjects affected / exposed	1 / 383 (0.26%)	12 / 383 (3.13%)	
occurrences (all)	1	18	
Oedema peripheral			
subjects affected / exposed	7 / 383 (1.83%)	5 / 383 (1.31%)	
occurrences (all)	12	7	
Chest pain			
subjects affected / exposed	1 / 383 (0.26%)	8 / 383 (2.09%)	
occurrences (all)	1	9	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 383 (0.52%)	5 / 383 (1.31%)	
occurrences (all)	3	7	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 383 (0.78%)	3 / 383 (0.78%)	
occurrences (all)	5	6	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 383 (0.26%)	6 / 383 (1.57%)	
occurrences (all)	2	8	
Insomnia			

subjects affected / exposed	5 / 383 (1.31%)	1 / 383 (0.26%)	
occurrences (all)	6	1	
Investigations			
Weight decreased			
subjects affected / exposed	26 / 383 (6.79%)	34 / 383 (8.88%)	
occurrences (all)	40	52	
Weight increased			
subjects affected / exposed	3 / 383 (0.78%)	4 / 383 (1.04%)	
occurrences (all)	3	11	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 383 (2.09%)	21 / 383 (5.48%)	
occurrences (all)	9	39	
Peripheral sensory neuropathy			
subjects affected / exposed	12 / 383 (3.13%)	26 / 383 (6.79%)	
occurrences (all)	15	41	
Dizziness			
subjects affected / exposed	6 / 383 (1.57%)	14 / 383 (3.66%)	
occurrences (all)	7	16	
Paraesthesia			
subjects affected / exposed	4 / 383 (1.04%)	11 / 383 (2.87%)	
occurrences (all)	4	13	
Dysgeusia			
subjects affected / exposed	5 / 383 (1.31%)	8 / 383 (2.09%)	
occurrences (all)	5	11	
Tremor			
subjects affected / exposed	0 / 383 (0.00%)	4 / 383 (1.04%)	
occurrences (all)	0	5	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	30 / 383 (7.83%)	70 / 383 (18.28%)	
occurrences (all)	59	184	
Thrombocytopenia			
subjects affected / exposed	10 / 383 (2.61%)	10 / 383 (2.61%)	
occurrences (all)	18	28	
Anaemia			

subjects affected / exposed	9 / 383 (2.35%)	3 / 383 (0.78%)	
occurrences (all)	12	3	
Leukopenia			
subjects affected / exposed	4 / 383 (1.04%)	3 / 383 (0.78%)	
occurrences (all)	7	4	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	7 / 383 (1.83%)	4 / 383 (1.04%)	
occurrences (all)	9	6	
Conjunctivitis			
subjects affected / exposed	6 / 383 (1.57%)	0 / 383 (0.00%)	
occurrences (all)	9	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	80 / 383 (20.89%)	104 / 383 (27.15%)	
occurrences (all)	123	208	
Abdominal pain			
subjects affected / exposed	48 / 383 (12.53%)	99 / 383 (25.85%)	
occurrences (all)	165	273	
Constipation			
subjects affected / exposed	10 / 383 (2.61%)	96 / 383 (25.07%)	
occurrences (all)	19	181	
Vomiting			
subjects affected / exposed	44 / 383 (11.49%)	81 / 383 (21.15%)	
occurrences (all)	64	126	
Stomatitis			
subjects affected / exposed	39 / 383 (10.18%)	82 / 383 (21.41%)	
occurrences (all)	62	156	
Diarrhoea			
subjects affected / exposed	96 / 383 (25.07%)	70 / 383 (18.28%)	
occurrences (all)	234	138	
Abdominal pain upper			
subjects affected / exposed	11 / 383 (2.87%)	39 / 383 (10.18%)	
occurrences (all)	21	77	
Dyspepsia			

subjects affected / exposed	3 / 383 (0.78%)	8 / 383 (2.09%)	
occurrences (all)	3	9	
Abdominal distension			
subjects affected / exposed	5 / 383 (1.31%)	9 / 383 (2.35%)	
occurrences (all)	7	13	
Dry mouth			
subjects affected / exposed	3 / 383 (0.78%)	7 / 383 (1.83%)	
occurrences (all)	3	11	
Gastritis			
subjects affected / exposed	5 / 383 (1.31%)	5 / 383 (1.31%)	
occurrences (all)	8	7	
Oral pain			
subjects affected / exposed	1 / 383 (0.26%)	6 / 383 (1.57%)	
occurrences (all)	1	8	
Flatulence			
subjects affected / exposed	2 / 383 (0.52%)	4 / 383 (1.04%)	
occurrences (all)	2	4	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 383 (0.00%)	5 / 383 (1.31%)	
occurrences (all)	0	6	
Hyperbilirubinaemia			
subjects affected / exposed	10 / 383 (2.61%)	4 / 383 (1.04%)	
occurrences (all)	15	10	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	180 / 383 (47.00%)	89 / 383 (23.24%)	
occurrences (all)	571	222	
Alopecia			
subjects affected / exposed	3 / 383 (0.78%)	41 / 383 (10.70%)	
occurrences (all)	3	48	
Nail disorder			
subjects affected / exposed	9 / 383 (2.35%)	11 / 383 (2.87%)	
occurrences (all)	11	15	
Rash			

subjects affected / exposed	6 / 383 (1.57%)	7 / 383 (1.83%)	
occurrences (all)	6	8	
Dry skin			
subjects affected / exposed	10 / 383 (2.61%)	7 / 383 (1.83%)	
occurrences (all)	14	11	
Erythema			
subjects affected / exposed	2 / 383 (0.52%)	6 / 383 (1.57%)	
occurrences (all)	2	9	
Skin hyperpigmentation			
subjects affected / exposed	7 / 383 (1.83%)	1 / 383 (0.26%)	
occurrences (all)	8	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 383 (0.78%)	30 / 383 (7.83%)	
occurrences (all)	3	55	
Myalgia			
subjects affected / exposed	4 / 383 (1.04%)	27 / 383 (7.05%)	
occurrences (all)	4	48	
Pain in extremity			
subjects affected / exposed	3 / 383 (0.78%)	20 / 383 (5.22%)	
occurrences (all)	7	42	
Bone pain			
subjects affected / exposed	1 / 383 (0.26%)	7 / 383 (1.83%)	
occurrences (all)	1	21	
Musculoskeletal pain			
subjects affected / exposed	1 / 383 (0.26%)	10 / 383 (2.61%)	
occurrences (all)	1	12	
Pain in jaw			
subjects affected / exposed	0 / 383 (0.00%)	7 / 383 (1.83%)	
occurrences (all)	0	23	
Muscle spasms			
subjects affected / exposed	3 / 383 (0.78%)	4 / 383 (1.04%)	
occurrences (all)	3	7	
Back pain			

subjects affected / exposed	3 / 383 (0.78%)	4 / 383 (1.04%)	
occurrences (all)	6	6	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 383 (1.04%)	3 / 383 (0.78%)	
occurrences (all)	4	3	
Bronchitis			
subjects affected / exposed	1 / 383 (0.26%)	4 / 383 (1.04%)	
occurrences (all)	1	4	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	23 / 383 (6.01%)	42 / 383 (10.97%)	
occurrences (all)	29	78	
Dehydration			
subjects affected / exposed	5 / 383 (1.31%)	3 / 383 (0.78%)	
occurrences (all)	6	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2009	Implementation of the revised RECIST guideline version 1.1 (instead of the previous version 1.0), Introduction of systematic antiemetic prophylaxis guidelines, Modification of constipation prophylaxis Deletion of unnecessary biological exams such as prothrombin time or partial thromboplastin time replaced by the INR for patients on coumadin or warfarin, Modification of treatment labelling.
07 December 2009	Modification of recommendations for capecitabine dose adjustment in consistency with a new version of Xeloda SmPC, Minimum delay between discontinuation of the anti-HER-2 therapy and randomisation shortened from 4 to 3 weeks, Clarification of inclusion criteria about resistance to taxane therapy (restricted to patient with at least 2 cycles of taxane-based therapy), Clarification about acceptable imaging based procedures for confirmation of bone lesions (CT-scan, MRI and X-ray), • Addition of dose adaptation rules for total bilirubin level increase, • Update of the number of expected participating countries and sites"
19 May 2011	Modification of the inclusion criteria number 15, limiting the inclusion to patients of less than 80 year-old in agreement with recent results and modification of the Javlor SmPC, Modification of secondary efficacy analysis with pooling of 3 independent factors (hormonal receptor to oestrogen status, hormonal receptor to progesterone status and HER-2 status) for PFS, OS and ORR multivariate analysis."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported