Clinical trial results:
A Randomized Phase II Study of Two Chemotherapy Regimens, Pemetrexed-Carboplatin, and Gemcitabine-Vinorelbine, in Anthracycline and Taxanes Pretreated Advanced Breast Cancer Patients

Summary

EudraCT number	2006-000441-19
Trial protocol	DE ES IT
Global end of trial date	27 August 2010

Results information

Result version number	v1 (current)
This version publication date	15 April 2016
First version publication date	15 April 2016

Trial information

Trial identification

Sponsor protocol code	H3E-EW-S098

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00325234
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Alias: H3E-EW-S098, Trial ID: 10826

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM, Eli Lilly and Company, 1 800-877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM, Eli Lilly and Company, 1 800-285-4559,

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	27 August 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 August 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to help answer the following research questions:
•whether the chemotherapy combination therapy Pemetrexed-Carboplatin or Gemcitabine-Vinorelbine can help participants with advanced breast cancer to make the tumor smaller or disappear and for how long
•to learn more about the side effects in each chemotherapy combination treatment arm
•to assess how participants with advanced breast cancer report health changes while receiving any of the chemotherapy combination arm

Protection of trial subjects:

This study was conducted in accordance with International Code of Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Switzerland: 9
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	South Africa: 13
Worldwide total number of subjects	135
EEA total number of subjects	87

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)	115
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Not Applicable

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pemetrexed/Carboplatin

Arm description:

Pemetrexed 600 milligram per meter squared (mg/m^2) was administered intravenously over approximately 10 minutes on Day 1. Carboplatin was given over approximately 30 minutes on Day 1 beginning after the end of the Pemetrexed infusion, consistent with a target of AUC 5.0 milligram/minute/millilter (mg*min/mL). The cycle of treatment was 21 days

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	LY231514, Alimta
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed 600 mg/m^2, administered intravenously (IV) every 21 days until disease progression or unacceptable toxicity.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was given over approximately 30 minutes on Day 1 beginning after the end of the Pemetrexed infusion, consistent with a target of AUC 5.0 mg*min/mL. The cycle of treatment was 21 days until disease progression or unacceptable toxicity.

Arm title	Gemcitabine/Vinorelbine

Arm description:

Vinorelbine 30 mg/m^2 was given over approximately 6-10 minutes on Day 1 and Day 8.

Gemcitabine 1200 mg/m^2 was given over approximately 30 minutes on Day 1 and Day 8 beginning after the end of the Vinorelbine infusion. The cycle of treatment was 21 days.

Arm type	Active comparator
Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: 30 mg/m^2 vinorelbine administered IV on day 1 and day 8 every 21 days until disease progression or unacceptable toxicity.	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	LY188011, Gemzar
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 1200 mg/m^2 gemcitabine, administered IV on day 1 and day 8 every 21 days until disease progression or unacceptable toxicity.	

Number of subjects in period 1	Pemetrexed/Carboplatin	Gemcitabine/Vinorelbine
Started	69	66
Received at Least 1 Dose of Study Drug	65	66
Completed	0	0
Not completed	69	66
'Death due to Study Disease '	1	-
Physician decision	17	12
Subject Decision	6	8
Adverse event, non-fatal	10	7
'Progressive Disease '	34	37
Entry Criteria Not Met	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Pemetrexed/Carboplatin
Reporting group description:	
Pemetrexed 600 milligram per meter squared (mg/m^2) was administered intravenously over approximately 10 minutes on Day 1. Carboplatin was given over approximately 30 minutes on Day 1 beginning after the end of the Pemetrexed infusion, consistent with a target of AUC 5.0 milligram/minute/millilter (mg*min/mL). The cycle of treatment was 21 days	
Reporting group title	Gemcitabine/Vinorelbine
Reporting group description:	
Vinorelbine 30 mg/m^2 was given over approximately 6-10 minutes on Day 1 and Day 8. Gemcitabine 1200 mg/m^2 was given over approximately 30 minutes on Day 1 and Day 8 beginning after the end of the Vinorelbine infusion. The cycle of treatment was 21 days.	

Reporting group values	Pemetrexed/Carboplatin	Gemcitabine/Vinorelbine	Total
Number of subjects	69	66	135
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	51.9	52.3	
standard deviation	± 11.38	± 10.4	-
Gender categorical Units: Subjects			
Female	69	66	135
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	67	61	128
African	1	3	4
Hispanic	0	1	1
East Asian	1	0	1
West Asian	0	1	1
Region of Enrollment Units: Subjects			
Spain	18	18	36
Switzerland	5	4	9
Israel	9	9	18
Germany	9	12	21
Italy	16	14	30
Turkey	5	3	8
South Africa	7	6	13
Eastern Cooperative Oncology Group (ECOG) Performance Status			
The Eastern Cooperative Oncology Group (ECOG) scales and criteria are used by doctors to assess disease progression, assess the patient's living ability, and determine prognosis. The scale is as follows:			

0-Fully active, able to carry on all pre-disease performance without restriction. 1-Restricted in activity but ambulatory and able to perform sedentary work. 2-Ambulatory but unable to work. Up and about > 50% of waking hours. 3-Capable of only limited selfcare, confined to bed or chair > 50% of waking hours. 4-Completely disabled. Cannot self care. Totally confined to bed or chair. 5-Dead.			
Units: Subjects			
ECOG 0	39	39	78
ECOG 1	28	27	55
ECOG 2	2	0	2
Hormonal Receptor Status			
Hormone receptor status is a positive or negative measure of estrogen (ER) or progesterone (PR) hormone receptors found in cancer cells. In hormone receptor negative tumors, estrogen and/or progesterone are not present in cancer cells. In hormone receptor positive tumors, estrogen and/or progesterone hormone receptors are present in the cancer cells.			
Units: Subjects			
Estrogen and Progesterone Negative	19	21	40
Estrogen and/or Progesterone Positive	49	44	93
Unknown	1	1	2
Human Epidermal Growth Factor Receptor 2 (HER-2/Neu)			
The Human Epidermal Growth Factor Receptor 2 plays an important role in cell growth and development. HER-2/Neu status is determined by an assay. A positive HER-2/Neu result indicates that HER-2 gene receptors are present; negative HER-2/Neu indicates the absence of HER-2 gene receptors.			
Units: Subjects			
Positive	12	13	25
Negative	53	49	102
Not Performed	0	1	1
Unknown	4	3	7
Tumor Differentiation Grade			
Classification of tumors into one of four grades based upon how similar in appearance the tumor cells are to normal cells, and by how many tumor cells are dividing. The more tumor cells that are dividing, the greater likelihood of tumor growth and the higher the tumor grade. A lower tumor grade is associated with a better prognosis. Grade 1 - Well-Differentiated, Low cell division Grade 2 - Moderately Differentiated, Moderate cell division Grade 3 - Poorly Differentiated, High cell division Grade 4 - Undifferentiated, High cell division			
Units: Subjects			
Grade I	6	3	9
Grade II	25	27	52
Grade III	32	30	62
Unknown	6	6	12
Pathological Diagnosis			
This measure is the specific diagnosis of breast cancer based upon pathological diagnosis.			
Units: Subjects			
Carcinoma, Ductal, Breast	64	54	118
Carcinoma, Lobular, Breast	4	5	9
Carcinoma, Inflammatory, Breast	1	3	4
Carcinoma, Mixed Cell, Breast	0	1	1
Other	0	3	3

End points

End points reporting groups

Reporting group title	Pemetrexed/Carboplatin

Reporting group description:

Pemetrexed 600 milligram per meter squared (mg/m^2) was administered intravenously over approximately 10 minutes on Day 1. Carboplatin was given over approximately 30 minutes on Day 1 beginning after the end of the Pemetrexed infusion, consistent with a target of AUC 5.0 milligram/minute/millilter (mg*min/mL). The cycle of treatment was 21 days

Reporting group title	Gemcitabine/Vinorelbine

Reporting group description:

Vinorelbine 30 mg/m^2 was given over approximately 6-10 minutes on Day 1 and Day 8.

Gemcitabine 1200 mg/m^2 was given over approximately 30 minutes on Day 1 and Day 8 beginning after the end of the Vinorelbine infusion. The cycle of treatment was 21 days.

Primary: Tumor Response Rate

End point title	Tumor Response Rate[1]

End point description:

Participants with best overall response determined from complete response (CR) or partial response (PR) according to Response Criteria in Solid Tumors (RECIST) criteria. For CR or PR, best response must be confirmed. A second assessment performed at 28 days. Two determinations of CR before progression required for rate to=CR. Evaluations include: CR=Disappearance of lesions. PR=≥30% size decrease of lesions. Progressive Disease (PD)=≥20% size increase of lesions. Stable Disease (SD)=Not enough shrinkage for PR nor enough increase for PD. Overall Response Rate=PR+CR/Qualified Participants*100.

End point type	Primary

End point timeframe:

Baseline up to 30 days of follow-up after 21 cycles of treatment.

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: There is no statistical analysis for the primary endpoint of Tumor Response Rate. Descriptive statistics are used to represent the tumor response in each treatment arm and reported as percentage of participants with a 95% confidence interval.

End point values	Pemetrexed/Carboplatin	Gemcitabine/Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	61		
Units: Participants				
number (confidence interval 95%)				
Overall Response	26.6 (16.3 to 39.1)	29.5 (18.5 to 42.6)		
Complete Response	0 (0 to 5.6)	3.3 (0.4 to 11.3)		
Partial Response	26.6 (16.3 to 39.1)	26.2 (15.8 to 39.1)		
Stable Disease	35.9 (24.3 to 48.9)	34.4 (22.7 to 47.7)		
Progressive Disease	26.6 (16.3 to 39.1)	27.9 (17.1 to 40.8)		
Unknown	10.9 (4.5 to 21.2)	8.2 (2.7 to 18.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR-RECIST criteria of (Complete Response [CR =Disappearance of lesions] or Partial Response [PR=≥30% size decrease of lesions]) is defined as time from the date when measurement criteria are met for CR or PR until the date of first observation of progressive disease (PD) or death from study disease. For participants who die from causes other than study disease and without PD, DOR will be censored at the date of death. For participants who have not died as of the data cut-off date who are without PD, DOR was censored at last contact date.

End point type	Secondary

End point timeframe:

Time of response to progressive disease (up to 19 months) .

End point values	Pemetrexed/Carboplatin	Gemcitabine/Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: Months				
median (confidence interval 95%)				
Duration of Response	7.7 (4.2 to 12.2)	7.5 (4.9 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progressive Disease (PD)

End point title	Time to Progressive Disease (PD)

End point description:

Time to PD is defined as the time from the date of study enrollment to the first documented date of PD or death from study disease. For participants who die from causes other than study disease and without PD, time to PD was censored at the date of death. For participants not known to have died as of the data cut-off date and do not have PD, time to PD was censored at the last contact date. For participants who received subsequent chemotherapy (after discontinuation from the study chemotherapy) prior to disease progression, time to PD was censored at the date of subsequent chemotherapy.

End point type	Secondary

End point timeframe:

Baseline to measured PD (up to 25.1 months).

End point values	Pemetrexed/Carboplatin	Gemcitabine/Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: Months				
median (confidence interval 95%)				
Time to Progressive Disease (PD)	5.1 (4.1 to 8)	5.6 (4.2 to 7.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Treatment Failure (TTTF)

End point title	Time To Treatment Failure (TTTF)

End point description:

TTTF is defined as the time from date of study enrollment to the first documented date of death, PD, or study treatment discontinuation due to adverse event (AE). For participants not known to have discontinued as of the data cut-off date, TTTF is censored at the last contact date. For participants who discontinued for reasons other than death, PD, or AE, TTTF is censored at the date of discontinuation.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (up to 21.9 months).

End point values	Pemetrexed/Carboplatin	Gemcitabine/Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: Months				
median (confidence interval 95%)				
Time To Treatment Failure (TTTF)	4.8 (3.3 to 7)	5.1 (3.5 to 6.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response (Complete Response(CR) or Partial Response (PR) is defined as the time from the date of study enrollment to the first date when the measurement criteria are met for complete response or partial response (whichever status is recorded first). CR=Disappearance of target lesions lesions. PR=≥30% size decrease of lesions.

End point type	Secondary

End point timeframe:

Baseline to response (up to 7.8 months).

End point values	Pemetrexed/Carboplatin	Gemcitabine/Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: Months				
median (confidence interval 95%)				
Time to Response	1.8 (1.6 to 3.3)	1.8 (1.6 to 3.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AE)

End point title	Number of Participants With Adverse Events (AE)

End point description:

A listing of adverse events is presented in the Reported Adverse Event Module.

End point type	Secondary

End point timeframe:

Every cycle up to twenty-one 21-day cycles (plus 30 days of follow-up)

End point values	Pemetrexed/Carboplatin	Gemcitabine/Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	66		
Units: Participants				
number (not applicable)				
Adverse Events	64	66		
Serious Adverse Events	18	22		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

H3E-EW-S098

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Arm B: Vinorelbine plus Gemcitabine

Reporting group description: -

Reporting group title	Arm A: Pemetrexed plus Carboplatin

Reporting group description: -

Serious adverse events	Arm B: Vinorelbine plus Gemcitabine	Arm A: Pemetrexed plus Carboplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 66 (33.33%)	19 / 65 (29.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
metastases to central nervous system			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (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			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
subclavian vein thrombosis			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (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			
condition aggravated			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
medical device complication			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
performance status decreased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	3 / 66 (4.55%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea exertional			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pharyngeal inflammation			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
alanine aminotransferase increased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood glucose increased			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
international normalised ratio increased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ankle fracture			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
femur fracture			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
joint dislocation			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiac failure congestive			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
epilepsy			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	5 / 65 (7.69%)	
occurrences causally related to treatment / all	0 / 1	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	2 / 66 (3.03%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
leukocytosis			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	2 / 66 (3.03%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	2 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombocytopenia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	6 / 65 (9.23%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
epigastric discomfort			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
hepatic failure			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
jaundice			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
rash			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
breast cellulitis			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
implant site infection			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
staphylococcal sepsis			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
streptococcal infection			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound infection			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypercalcaemia			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	0 / 66 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm B: Vinorelbine plus Gemcitabine	Arm A: Pemetrexed plus Carboplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 66 (100.00%)	62 / 65 (95.38%)	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	21 / 66 (31.82%)	11 / 65 (16.92%)	
occurrences (all)	30	16	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	17 / 66 (25.76%)	9 / 65 (13.85%)	
occurrences (all)	25	14	
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	7 / 66 (10.61%)	7 / 65 (10.77%)	
occurrences (all)	8	7	
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	11 / 66 (16.67%)	4 / 65 (6.15%)	
occurrences (all)	16	4	
weight decreased			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	8 / 66 (12.12%)	3 / 65 (4.62%)	
occurrences (all)	8	3	
Vascular disorders			
phlebitis			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	6 / 66 (9.09%)	0 / 65 (0.00%)	
occurrences (all)	8	0	
Cardiac disorders			
palpitations			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	5 / 66 (7.58%)	1 / 65 (1.54%)	
occurrences (all)	5	1	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	4 / 66 (6.06%)	5 / 65 (7.69%)	
occurrences (all)	4	7	
dysgeusia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	4 / 66 (6.06%)	3 / 65 (4.62%)	
occurrences (all)	4	3	
headache			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	11 / 66 (16.67%)	7 / 65 (10.77%)	
occurrences (all)	16	10	
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	9 / 66 (13.64%)	3 / 65 (4.62%)	
occurrences (all)	14	3	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	13 / 66 (19.70%)	14 / 65 (21.54%)	
occurrences (all)	19	23	
fatigue			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	26 / 66 (39.39%)	23 / 65 (35.38%)	
occurrences (all)	39	38	
oedema peripheral			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	6 / 66 (9.09%)	6 / 65 (9.23%)	
occurrences (all)	7	6	
pyrexia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	21 / 66 (31.82%)	5 / 65 (7.69%)	
occurrences (all)	33	6	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	28 / 66 (42.42%)	32 / 65 (49.23%)	
occurrences (all)	36	46	
leukopenia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	35 / 66 (53.03%)	28 / 65 (43.08%)	
occurrences (all)	84	79	
lymphopenia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	8 / 66 (12.12%)	10 / 65 (15.38%)	
occurrences (all)	15	13	
neutropenia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	51 / 66 (77.27%)	37 / 65 (56.92%)	
occurrences (all)	154	120	
thrombocytopenia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	11 / 66 (16.67%)	17 / 65 (26.15%)	
occurrences (all)	23	34	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	9 / 66 (13.64%)	3 / 65 (4.62%)	
occurrences (all)	12	3	
abdominal pain upper			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	10 / 66 (15.15%)	5 / 65 (7.69%)	
occurrences (all)	13	5	
diarrhoea			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	12 / 66 (18.18%)	7 / 65 (10.77%)	
occurrences (all)	14	7	
constipation			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	26 / 66 (39.39%)	18 / 65 (27.69%)	
occurrences (all)	41	24	
dysphagia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 66 (1.52%)	4 / 65 (6.15%)	
occurrences (all)	1	5	
dyspepsia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	6 / 66 (9.09%)	2 / 65 (3.08%)	
occurrences (all)	7	3	
nausea			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	23 / 66 (34.85%)	31 / 65 (47.69%)	
occurrences (all)	73	48	
vomiting			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	15 / 66 (22.73%)	15 / 65 (23.08%)	
occurrences (all)	19	20	
stomatitis			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	11 / 66 (16.67%)	7 / 65 (10.77%)	
occurrences (all)	12	8	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	9 / 66 (13.64%)	5 / 65 (7.69%)	
occurrences (all)	11	5	
epistaxis			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	2 / 66 (3.03%)	5 / 65 (7.69%)	
occurrences (all)	2	6	
dyspnoea			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	6 / 66 (9.09%)	4 / 65 (6.15%)	
occurrences (all)	7	4	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	16 / 66 (24.24%)	8 / 65 (12.31%)	
occurrences (all)	16	8	
pruritus			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	7 / 66 (10.61%)	6 / 65 (9.23%)	
occurrences (all)	7	11	
rash			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	9 / 66 (13.64%)	4 / 65 (6.15%)	
occurrences (all)	10	4	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	6 / 66 (9.09%)	1 / 65 (1.54%)	
occurrences (all)	6	1	
insomnia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	3 / 66 (4.55%)	6 / 65 (9.23%)	
occurrences (all)	3	6	
Musculoskeletal and connective tissue disorders			

arthralgia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	5 / 66 (7.58%)	2 / 65 (3.08%)	
occurrences (all)	9	2	
back pain			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	6 / 66 (9.09%)	5 / 65 (7.69%)	
occurrences (all)	17	5	
musculoskeletal pain			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	6 / 66 (9.09%)	4 / 65 (6.15%)	
occurrences (all)	8	4	
pain in extremity			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	5 / 66 (7.58%)	0 / 65 (0.00%)	
occurrences (all)	6	0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	12 / 66 (18.18%)	8 / 65 (12.31%)	
occurrences (all)	13	10	
hyperglycaemia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	5 / 66 (7.58%)	3 / 65 (4.62%)	
occurrences (all)	5	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2007	Changed inclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported