Clinical trial results:
A Phase 1/Randomized Phase 2 Study to Evaluate LY2603618 in Combination with Pemetrexed and Cisplatin in Patients with Stage IV Non-small Cell Lung Cancer

Summary

EudraCT number	2010-020408-31
Trial protocol	DE
Global end of trial date	04 September 2014

Results information

Result version number	v1 (current)
This version publication date	05 January 2018
First version publication date	05 January 2018

Trial information

Trial identification

Sponsor protocol code	I2I-MC-JMMG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01139775
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 13797

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 EST, Eli Lilly and Company, +1 877-CTLILLY,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, +1 877-285-4559,

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	04 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the Phase 1 part determination of the recommended Phase 2 dose of LY2603618. Primary objective of the Phase 2 part are Determination if the progression-free survival (PFS) time, from the date of randomization to induction therapy, is improved for participants with Stage IV nonsquamous NSCLC when LY2603618 is added to the first-line therapy of 4 cycles of pemetrexed and cisplatin followed by maintenance therapy of pemetrexed
with or without LY2603618
Due to the dosing regimen changes, subgroup analysis on participants who were treated per JMMG Amendemnt (c) will be performed for PFS.

Protection of trial subjects:

This study was conducted in accordance with International Conference on 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	11 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 43
Country: Number of subjects enrolled	Germany: 33
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	59
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Entered

Pre-assignment

Screening details:

No Text Entered

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: Pemetrexed + Cisplatin + LY2603618

Arm description:

Cycles 1-2 (21-day cycle):
Day 1: pemetrexed 500 milligrams per meter square (mg/m^2) + cisplatin 75 mg/m^2

Day 2: LY2603618 at 130-275 milligrams (mg)

After 2 cycles, participants may continue on study drug until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

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

Dosage and administration details:

Administered intravenously as a continuous 10-minute infusion

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

Dosage and administration details:

Administered intravenously as a continuous 1-hour infusion

Investigational medicinal product name	LY2603618
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously as a continuous 1-hour infusion

Arm title	Phase 2: Pemetrexed + Cisplatin + LY2603618

Arm description:

Cycles 1-4 (21-day cycle):
Before 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

Day 2: LY2603618 dose from phase 1 portion of trial

After 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

After 4 cycles, participants may continue on maintenance therapy until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

Maintenance Therapy Experimental Arm (every 21 days):

Before 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2

Day 2: LY2603618 dose determined from phase 1

After 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2

If, as of 25 Oct 2012, participant was in maintenance therapy and randomized to the experimental arm, the participant is eligible to continue with pemetrexed (Day 1)/LY2603618 (Day 2) therapy if the investigator deems it is in the best interest of the participant and the participant consents.

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Administered intravenously as a continuous 10-minute infusion	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Administered intravenously as a continuous 1-hour infusion	
Investigational medicinal product name	LY2603618
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Administered intravenously as a continuous 1-hour infusion	
Arm title	Phase 2: Pemetrexed + Cisplatin

Arm description:

Cycle 1-4 (21-day cycle)
Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

After 4 cycles, participants may continue on maintenance therapy until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

Maintenance Therapy Comparator Arm: Phase 2 (every 21 days):

Day 1: pemetrexed 500 mg/m^2

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

Dosage and administration details:

Cycles 1-4 (21-day cycle):

Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

After 4 cycles, participants may have continued on maintenance therapy until disease progression, unacceptable toxicity, or other withdrawal criterion was met.

Maintenance therapy (every 21 days):

Day 1: pemetrexed 500 mg/m^2

Pemetrexed was administered IV over 10 minutes, and cisplatin was administered IV over 1 hour.

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

Dosage and administration details:

Cisplatin 75 milligrams per meter squared

Number of subjects in period 1	Phase 1: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin
Started	14	39	23
Received at least one dose of study drug	14	39	22
Completed	13	26	17
Not completed	1	13	6
Consent withdrawn by subject	1	-	2
Physician decision	-	2	2
Adverse event, non-fatal	-	6	2
Protocol deviation	-	5	-

Baseline characteristics

Reporting groups

Reporting group title	Phase 1: Pemetrexed + Cisplatin + LY2603618

Reporting group description:

Cycles 1-2 (21-day cycle):
Day 1: pemetrexed 500 milligrams per meter square (mg/m^2) + cisplatin 75 mg/m^2

Day 2: LY2603618 at 130-275 milligrams (mg)

After 2 cycles, participants may continue on study drug until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

Reporting group title	Phase 2: Pemetrexed + Cisplatin + LY2603618

Reporting group description:

Cycles 1-4 (21-day cycle):
Before 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

Day 2: LY2603618 dose from phase 1 portion of trial

After 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

After 4 cycles, participants may continue on maintenance therapy until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

Maintenance Therapy Experimental Arm (every 21 days):

Before 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2

Day 2: LY2603618 dose determined from phase 1

After 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2

If, as of 25 Oct 2012, participant was in maintenance therapy and randomized to the experimental arm, the participant is eligible to continue with pemetrexed (Day 1)/LY2603618 (Day 2) therapy if the investigator deems it is in the best interest of the participant and the participant consents.

Reporting group title	Phase 2: Pemetrexed + Cisplatin

Reporting group description:

Cycle 1-4 (21-day cycle)
Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

After 4 cycles, participants may continue on maintenance therapy until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

Maintenance Therapy Comparator Arm: Phase 2 (every 21 days):

Day 1: pemetrexed 500 mg/m^2

Reporting group values	Phase 1: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin

Number of subjects	14	39	23
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
geometric mean	57.9	57.9	56.4
standard deviation	± 11.4	± 10.1	± 9.8
Gender categorical Units: Subjects			
Female	7	15	8
Male	7	24	15
Region of Enrollment Units: Subjects			
Spain	7	24	12
Germany	7	15	11
Initial Pathological Diagnosis Units: Subjects			
Adenocarcinoma, Bronchiolalveolar	0	0	1
Adenocarcinoma, Colon	1	0	0
Adenocarcinoma, Lung	8	38	19
Adenocarcinoma, Moderately Diff., Lung	0	0	1
Carcinoma, Ampulla of Vater	1	0	0
Carcinoma, Breast	1	0	0
Carcinoma, Large Cell, Lung	0	0	1
Carcinoma, Lung	0	1	0
Carcinoma, Non-small Cell, Poorly Diff, Lung	1	0	0
Carcinoma, Pancreas	1	0	0
Mesothelioma, Malignum	1	0	0
Pleuritis Carcinomatosa	0	0	1
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Measure Description: Eastern Cooperative Oncology Group (ECOG) Performance Status classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death) as follows: 0 - Fully Active; 1 - Ambulatory, Restricted Strenuous Activity; 2 - Ambulatory, No Work Activities; 3 - Partially Confined to Bed, Limited Self Care; 4 - Completely Disabled; and 5 - Dead.			
Units: Subjects			
ECOG Status 0	11	9	7
ECOG Status 1	3	30	15
Missing	0	0	1
Race/Ethnicity Units: Subjects			
White	14	39	23

Reporting group values	Total		
Number of subjects	76		
Age categorical Units: Subjects			
Adults (18-64 years)	0		

From 65-84 years	0		
85 years and over	0		

Age continuous			
Units: years			
geometric mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	30		
Male	46		
Region of Enrollment			
Units: Subjects			
Spain	43		
Germany	33		
Initial Pathological Diagnosis			
Units: Subjects			
Adenocarcinoma, Bronchiolalveolar	1		
Adenocarcinoma, Colon	1		
Adenocarcinoma, Lung	65		
Adenocarcinoma, Moderately Diff., Lung	1		
Carcinoma, Ampulla of Vater	1		
Carcinoma, Breast	1		
Carcinoma, Large Cell, Lung	1		
Carcinoma, Lung	1		
Carcinoma, Non-small Cell, Poorly Diff, Lung	1		
Carcinoma, Pancreas	1		
Mesothelioma, Malignum	1		
Pleuritis Carcinomatosa	1		
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Measure Description: Eastern Cooperative Oncology Group (ECOG) Performance Status classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death) as follows: 0 - Fully Active; 1 - Ambulatory, Restricted Strenuous Activity; 2 - Ambulatory, No Work Activities; 3 - Partially Confined to Bed, Limited Self Care; 4 - Completely Disabled; and 5 - Dead.			
Units: Subjects			
ECOG Status 0	27		
ECOG Status 1	48		
Missing	1		
Race/Ethnicity			
Units: Subjects			
White	76		

End points

End points reporting groups

Reporting group title	Phase 1: Pemetrexed + Cisplatin + LY2603618

Reporting group description:

Cycles 1-2 (21-day cycle):
Day 1: pemetrexed 500 milligrams per meter square (mg/m^2) + cisplatin 75 mg/m^2

Day 2: LY2603618 at 130-275 milligrams (mg)

After 2 cycles, participants may continue on study drug until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

Reporting group title	Phase 2: Pemetrexed + Cisplatin + LY2603618

Reporting group description:

Cycles 1-4 (21-day cycle):
Before 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

Day 2: LY2603618 dose from phase 1 portion of trial

After 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

After 4 cycles, participants may continue on maintenance therapy until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

Maintenance Therapy Experimental Arm (every 21 days):

Before 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2

Day 2: LY2603618 dose determined from phase 1

After 25 Oct 2012:

Day 1: pemetrexed 500 mg/m^2

If, as of 25 Oct 2012, participant was in maintenance therapy and randomized to the experimental arm, the participant is eligible to continue with pemetrexed (Day 1)/LY2603618 (Day 2) therapy if the investigator deems it is in the best interest of the participant and the participant consents.

Reporting group title	Phase 2: Pemetrexed + Cisplatin

Reporting group description:

Cycle 1-4 (21-day cycle)
Day 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

After 4 cycles, participants may continue on maintenance therapy until disease progression, unacceptable toxicity, or other withdrawal criterion is met.

Maintenance Therapy Comparator Arm: Phase 2 (every 21 days):

Day 1: pemetrexed 500 mg/m^2

Primary: Phase 2: Progression-Free Survival Time

End point title	Phase 2: Progression-Free Survival Time[1]

End point description:

Progression-free survival (PFS) time is defined as the time from the date of randomization to the first date of documented objective progressive disease (PD) or death from any cause. For participants who were not known to have had objective PD as of the data inclusion cut-off date for a particular analysis, PFS was censored at the date of the last objective progression-free disease assessments. For participants who took any subsequent systemic anticancer therapy prior to progression, PFS was censored at the date of the last objective progression-free disease assessment prior to the start date of any subsequent systemic anticancer therapy. PFS time was summarized using Kaplan-Meier estimates.

End point type	Primary

End point timeframe:

Randomization up to first date of PD or death from any cause (up to 6 months after the last participant entered treatment)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was for progression-free survival time for phase 2 participants only and phase 1 participants were not included.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	23[2]		
Units: months				
median (confidence interval 90%)	4.7 (4.2 to 7.1)	1.5 (1.3 to 2.9)		

Notes:

[2] - All randomized Phase 2 participants.

Statistical analyses

Statistical analysis title	Phase 2: Progression-Free Survival Time
Comparison groups	Phase 2: Pemetrexed + Cisplatin + LY2603618 v Phase 2: Pemetrexed + Cisplatin
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.96 [4]
Method	Bayesian Posterior Probability

Notes:

[3] - The analysis for comparing progression-free survival time between the treatment arms used a Bayesian Augmented Control model with a hierarchical random-effects distribution on treatment effects. The final model incorporated historical data from a completed Phase 3 study (NCT00789373) to augment the prospective control arm data.

[4] - Inference about survival was made using a Bayesian posterior probability. Pemetrexed + cisplatin + LY2603618 was considered superior to pemetrexed + cisplatin if the posterior probability of superiority exceeded 0.85.

Primary: Phase 1: Recommended Phase 2 Dose of LY2603618

End point title	Phase 1: Recommended Phase 2 Dose of LY2603618[5][6]

End point description:

The recommended Phase 2 dose for LY2603618 when administered approximately 24 hours after pemetrexed and cisplatin was based on the maximum tolerated dose (MTD) and achievement of predefined LY2603618 plasma systemic exposures targets (area under the LY2603618 plasma concentration versus time curve from time zero to infinity [AUC(0-∞)] >21,000 nanogram*hour/milliliter [ng*h/mL] and maximum LY2603618 plasma concentration [Cmax] >2000 nanograms/milliliter [ng/mL]).

End point type	Primary

End point timeframe:

Time of first dose to last dose

Notes:

[5] - 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: Statistical analysis was not provided for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for recommended phase 2 dose of LY2603618 for phase 1 participants only and phase 2 participants were not included.

End point values	Phase 1: Pemetrexed + Cisplatin + LY2603618			
Subject group type	Reporting group			
Number of subjects analysed	14[7]			
Units: milligrams	275			

Notes:

[7] - Phase 1 participants who received at least 1 dose of any of the study drugs.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival

End point title	Phase 2: Overall Survival[8]

End point description:

Overall survival (OS) time is defined as the time from the date of randomization to the date of death from any cause. For participants not known to have died as of the data cut-off date, OS time was censored at the last contact date the participant was known to be alive prior to the data cut-off date. OS was summarized using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

Randomization to the date of death from any cause through the time of study discontinuation (approximately 12 months after last participant was randomized)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for overall survival for phase 2 participants only and phase 1 participants were not included.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[9]	23[10]		
Units: months				
median (confidence interval 90%)	12.9 (9.3 to	6.6 (4.2 to		

	9999)	19.4)

Notes:

[9] - The upper bound of the 90% confidence interval was not calculable.

[10] - All randomized Phase 2 participants.

Statistical analyses

Statistical analysis title	Phase 2: Overall Survival
Comparison groups	Phase 2: Pemetrexed + Cisplatin + LY2603618 v Phase 2: Pemetrexed + Cisplatin
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2294 [11]
Method	Logrank

Notes:

[11] - The test of treatment effect was conducted at a 2-sided alpha level of 0.10.

Secondary: Phase 2: Overall Tumor Response Rate: Percentage of Participants Who Achieved a Confirmed Best Response of Completed Response (CR) or Partial Response (PR)

End point title	Phase 2: Overall Tumor Response Rate: Percentage of Participants Who Achieved a Confirmed Best Response of Completed Response (CR) or Partial Response (PR)[12]

End point description:

Overall response rate is the best response of CR or PR as classified by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST, v1.1) guidelines. CR is defined as the disappearance of all target and non-target lesions, normalization of tumor marker level of non-target lesions, and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimeter (mm). PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of non-target lesions or appearance of new lesions. Overall response rate is calculated as a total number of participants with CR or PR divided by the total number of participants with at least 1 measurable lesion, multiplied by 100.

End point type	Secondary

End point timeframe:

Randomization until date of disease progression (up to 6 months after the last participant was randomized)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for overall tumor response rate for phase 2 arms and phase 1 participants were not included.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	23[13]		
Units: percentage of participants				
number (confidence interval 90%)	43.6 (28 to 60)	21.7 (7 to 44)		

Notes:

[13] - All randomized Phase 2 participants.

Statistical analyses

Statistical analysis title	Phase 2: Overall Tumor Response Rate: Percentage o
Comparison groups	Phase 2: Pemetrexed + Cisplatin + LY2603618 v Phase 2: Pemetrexed + Cisplatin
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0824 [14]
Method	Chi-squared

Notes:

[14] - The test of treatment effect was conducted at a 2-sided alpha level of 0.10.

Secondary: Phase 2: Change in Tumor Size

End point title	Phase 2: Change in Tumor Size[15]

End point description:

Change in tumor size was based on tumor measurements collected according to RECIST, v1.1 guidelines. Tumor size is the sum of the tumor measurements (longest diameters) of target lesions at each tumor evaluation. Change in tumor size was defined as the change in log tumor size from baseline evaluation to the evaluation at the end of Cycle 2.

Analysis Population Description: Participants with measureable disease (target lesions) at baseline who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, end of Cycle 2

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was tumor size for phase 2 participants only and phase 1 participants were not included.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	22		
Units: centimeters				
arithmetic mean (standard deviation)	-0.3 (± 0.541)	-0.14 (± 0.277)		

Statistical analyses

Statistical analysis title	Phase 2: Change in Tumor Size
Comparison groups	Phase 2: Pemetrexed + Cisplatin + LY2603618 v Phase 2: Pemetrexed + Cisplatin

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4924 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - The test of treatment effect was conducted at a 2-sided alpha level of 0.10.

Secondary: Phase 1: Pharmacokinetic: Maximum Plasma Concentration (Cmax) (LY2603618)

End point title	Phase 1: Pharmacokinetic: Maximum Plasma Concentration (Cmax) (LY2603618)[17]

End point description:

Cmax is reported for each LY2603618 dose level on Cycle 1 /Day 2 and Cycle 2 /Day 2. The number of pharmacokinetic observations (n) used in the analysis is presented for each dose level and time point.

Analysis Population Description: Phase 1 participants who received at least 1 dose of LY2603618 and had samples collected for pharmacokinetic analysis.

End point type	Secondary

End point timeframe:

Cycle 1/Day 2 - immediately prior to end of LY2603618 infusion, and 1, 3, 6, 24, 48, 72, and 144 hours postdose; Cycle 2/Day 2 - predose, immediately prior to end of LY2603618 infusion, and 1, 3, 6, 24, 48, 72, and 144 hours postdose

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was maximum plasma concentration of LY2603618 in the phase 1 arm only and phase 2 participants were not included.

End point values	Phase 1: Pemetrexed + Cisplatin + LY2603618			
Subject group type	Reporting group			
Number of subjects analysed	13[18]			
Units: nanograms/milliliters				
geometric mean (geometric coefficient of variation)				
130 mg, Cycle 1/Day 2 (n=3)	1810 (± 14)			
130 mg, Cycle 2/Day 2 (n=3)	1730 (± 43)			
185 mg, Cycle 1/Day 2 (n=3)	2200 (± 33)			
185 mg, Cycle 2/Day 2 (n=3)	2190 (± 58)			
240 mg, Cycle 1/Day 2 (n=3)	3470 (± 27)			
240 mg, Cycle 2/Day 2 (n=3)	2750 (± 63)			
275 mg, Cycle 1/Day 2 (n=3)	4130 (± 29)			
275 mg, Cycle 2/Day 2 (n=4)	3620 (± 23)			

Notes:

[18] - Phase 1 participants who received at least 1 dose of LY2603618 and had samples collected for pharmac

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Pharmacokinetic: Cmax (Pemetrexed and Cisplatin)

End point title	Phase 1: Pharmacokinetic: Cmax (Pemetrexed and Cisplatin)[19]

End point description:

Cmax for pemetrexed and total platinum (t-platinum) from cisplatin is reported. The number of pharmacokinetic observations (n) used in the analysis is presented for each drug.

Analysis Population Description: Phase 1 participants who received at least 1 dose of pemetrexed or cisplatin and had samples collected for pharmacokinetic analysis.

End point type	Secondary

End point timeframe:

Pemetrexed: Cycle 1/Day 1 - immediately prior to end of pemetrexed infusion and 1, 2, 6 and 24 hours postdose. Cisplatin: Cycle 1/Day 1 - immediately prior to end of cisplatin infusion and 0.5, 1, 2, 6, 24, 72, 96, and 168 hours postdose.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was Cmax of pemetrexed and cisplatin in the phase 1 arm only and phase 2 participants were not included.

End point values	Phase 1: Pemetrexed + Cisplatin + LY2603618			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: nanograms/milliliters				
geometric mean (geometric coefficient of variation)				
Pemetrexed (n=14)	88300 (± 28)			
T-platinum from cisplatin (n=14)	3710 (± 43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Pharmacokinetic: Area Under the Plasma Concentration Versus Time Curve (AUC) (LY2603618)

End point title	Phase 1: Pharmacokinetic: Area Under the Plasma Concentration Versus Time Curve (AUC) (LY2603618)[20]

End point description:

AUC from time zero to 24 hours (AUC[0-24]), AUC from time zero to the last time point with a measurable concentration (AUC[0-tlast]), and AUC from time zero to infinity (AUC[0-∞]) values are reported for each LY2603618 dose level on Cycle 1 /Day 2 and Cycle 2 /Day 2. The number of pharmacokinetic observations (n) used in the analysis is presented for each dose level and time point.

Analysis Population Description: Phase 1 participants who received at least 1 dose of LY2603618 and had samples collected for pharmacokinetic analysis.

End point type	Secondary

End point timeframe:

Cycle 1/Day 2 - immediately prior to end of LY2603618 infusion and 1, 3, 6, 24, 48, 72, and 144 hours postdose; Cycle 2/Day 2 - predose, immediately prior to end of LY2603618 infusion, and 1, 3, 6, 24, 48, 72, and 144 hours postdose

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was for Area Under the Plasma Concentration Versus Time Curve of LY2603618 in the Phase 1 arm only and phase 2 participants were not included.

End point values	Phase 1: Pemetrexed + Cisplatin + LY2603618			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: nanogram*hour/milliliter				
geometric mean (geometric coefficient of variation)				
130 mg, Cycle 1/Day 2, AUC(0-24) (n=3)	8700 (± 30)			
130 mg, Cycle 2/Day 2, AUC(0-24) (n=3)	9780 (± 43)			
130 mg, Cycle 1/Day 1=2, AUC(0-tlast) (n=3)	10200 (± 26)			
130 mg, Cycle 2/Day 2, AUC(0-tlast) (n=3)	11300 (± 44)			
130 mg, Cycle 1/Day 2, AUC(0-∞) (n=3)	10200 (± 26)			
130 mg, Cycle 2/Day 2, AUC(0-∞) (n=3)	11300 (± 45)			
185 mg, Cycle 1/Day 2, AUC(0-24) (n=3)	13800 (± 119)			
185 mg, Cycle 2/Day 2, AUC(0-24) (n=3)	12500 (± 170)			
185 mg, Cycle 1/Day 2, AUC(0-tlast) (n=3)	18300 (± 192)			
185 mg, Cycle 2/Day 2, AUC(0-tlast) (n=3)	14800 (± 217)			
185 mg, Cycle 1/Day 2, AUC(0-∞) (n=3)	18400 (± 193)			
185 mg, Cycle 2/Day 2, AUC(0-∞) (n=3)	15700 (± 253)			
240 mg, Cycle 1/Day 2, AUC(0-24) (n=3)	26200 (± 19)			
240 mg, Cycle 2/Day 2, AUC(0-24) (n=3)	22100 (± 31)			
240 mg, Cycle 1/Day 2, AUC(0-tlast) (n=3)	32200 (± 21)			
240 mg, Cycle 2/Day 2, AUC(0-tlast) (n=3)	27300 (± 31)			
240 mg, Cycle 1/Day 2, AUC(0-∞) (n=3)	32300 (± 21)			
240 mg, Cycle 2/Day 2, AUC(0-∞) (n=3)	27500 (± 31)			
275 mg, Cycle 1/Day 2, AUC(0-24) (n=4)	28900 (± 24)			
275 mg, Cycle 2/Day 2, AUC(0-24) (n=4)	23500 (± 31)			
275 mg, Cycle 1/Day 2, AUC(0-tlast) (n=4)	38100 (± 36)			
275 mg, Cycle 2/Day 2, AUC(0-tlast) (n=4)	30800 (± 44)			
275 mg, Cycle 1/Day 2, AUC(0-∞) (n=4)	38300 (± 37)			
275 mg, Cycle 2/Day 2, AUC(0-∞) (n=4)	30900 (± 44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Pharmacokinetic: AUC (Pemetrexed and Cisplatin)

End point title	Phase 1: Pharmacokinetic: AUC (Pemetrexed and Cisplatin)[21]

End point description:

AUC(0-tlast) and AUC(0-∞) values are reported for pemetrexed and t-platinum from cisplatin. The number of pharmacokinetic observations (n) used in the analysis is presented for each drug.

Analysis Population Description: Phase 1 participants who received at least 1 dose of pemetrexed or cisplatin and had samples collected for pharmacokinetic analysis.

End point type	Secondary

End point timeframe:

Pemetrexed: Cycle 1/Day 1 - immediately prior to end of pemetrexed infusion and 1, 2, 6 and 24 hours postdose. Cisplatin: Cycle 1/Day 1 - immediately prior to end of cisplatin infusion and 0.5, 1, 2, 6, 24, 72, 96, and 168 hours postdose.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for Area Under the Concentration Time Curve of pemetrexed and t-platinum from cisplatin in the Phase 1 arm only and phase 2 participants were not included.

End point values	Phase 1: Pemetrexed + Cisplatin + LY2603618			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Pemetrexed, AUC(0-tlast) (n=14)	159000 (± 35)			
Pemetrexed, AUC (0-∞) (n=14)	160000 (± 35)			
T-platinum from cisplatin, AUC (0-tlast) (n=14)	163000 (± 26)			
T-platinum from cisplatin, AUC (0-∞) (n=14)	269000 (± 26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic: Cmax (LY2603618)

End point title	Phase 2: Pharmacokinetic: Cmax (LY2603618)[22]

End point description:

Analysis Population Description: Phase 2 participants who received at least 1 dose of LY2603618 and had samples collected for pharmacokinetic analysis.

End point type	Secondary

End point timeframe:

Cycle 1/Day 2 - predose, immediately prior to the end of the LY2603618 infusion, and 2-6, 24-48, and 72-96 hours postdose

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for Maximum Concentration of LY2603618 for the Phase 2 arm only and phase 1 (LY2603618) (and phase 2 pemetrexed and cisplatin) participants were not included.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	4130 (± 66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Pharmacokinetic: AUC (LY2603618)

End point title	Phase 2: Pharmacokinetic: AUC (LY2603618)[23]

End point description:

AUC (0-24), AUC(0-tlast), and AUC(0-∞) values are reported for LY2603618. The number of pharmacokinetic observations (n) used in the analysis is presented.

Analysis Population Description: Phase 2 participants who received at least 1 dose of LY2603618 and had samples collected for pharmacokinetic analysis.

End point type	Secondary

End point timeframe:

Cycle 1/Day 2 - predose, immediately prior to the end of the LY2603618 infusion, and 2-6, 24-48, and 72-96 hours postdose

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for Area Under the Concentration Time Curve of LY2603618 for the Phase 2 arm only and phase 1 (LY2603618) (and phase 2 pemetrexed and cisplatin) participants were not included.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ng*h/mL				
geometric mean (geometric coefficient				

of variation)				
AUC (0-24) (n=32)	31400 (± 49)			
AUC (0-tlast) (n=32)	39300 (± 58)			
AUC (0-∞) (n=31)	41100 (± 59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Change From Baseline to Long-term Follow up in Lung Cancer Symptom Scale (LCSS)

End point title	Phase 2: Change From Baseline to Long-term Follow up in Lung Cancer Symptom Scale (LCSS)[24]

End point description:

Health-related quality of life and participant symptoms were assessed using the LCSS (patient scale). However, improper implementation of questionnaires at the site level reduced the sponsor's ability to accurately evaluate the impacted data. Therefore, the LCSS data should be interpreted with caution.

The LCSS is a 9-item questionnaire. Six questions are symptom-specific measures for lung cancer (appetite, fatigue, cough, dyspnea, hemoptysis, and pain), and 3 summation items describe total symptomatic distress, activity status, and overall quality of life. Participant responses were measured using visual analogue scales (VAS) with 100-milliliter (mm) lines. Scores range from 0 (for best outcome) to 100 (for worst outcome). The Average Symptom Burden Index (ASBI) was calculated as the mean of 6 symptom-specific questions from the LCSS. The total LCSS score was calculated as the mean of 9 questions from the LCSS.

End point type	Secondary

End point timeframe:

Randomization to the end of study (approximately 12 months after the last participant entered treatment)

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for the phase 2 arms only; the LCSS was not administered to phase 1 participants.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[25]	22[26]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Total LCSS (n=32, 21)	-10.7 (± 14.1)	-11.7 (± 15.1)		
ASBI (n=34, 21)	-11.6 (± 13.9)	-12.6 (± 15.4)		

Notes:

[25] - All phase 2 participants with baseline (BL) LCSS assessment and at least 1 post-baseline assessment.
[26] - All phase 2 participants with baseline (BL) LCSS assessment and at least 1 post-baseline assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Document Any Antitumor Activity Per Radiological Scans and/or Tumor Markers

End point title	Phase 1: Document Any Antitumor Activity Per Radiological Scans and/or Tumor Markers[27]

End point description:

Overall response rate is presented. Overall response rate is defined as the percentage of participants with a best response of CR or PR as classified by the investigators according to RECIST, v1.1 criteria. CR is defined as the disappearance of all target and non-target lesions, normalization of tumor marker level of non-target lesions, and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of non-target lesions or appearance of new lesions. Overall response rate is calculated as a total number of participants with CR or PR divided by the total number of participants with at least 1 measurable lesion, multiplied by 100.

End point type	Secondary

End point timeframe:

Baseline through end of Phase 1

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for any antitumor activity for the phase 1 arm and phase 2 participants were not included.

End point values	Phase 1: Pemetrexed + Cisplatin + LY2603618			
Subject group type	Reporting group			
Number of subjects analysed	14[28]			
Units: percentage of participants				
arithmetic mean (confidence interval 90%)				
130 mg (N=3)	0 (0 to 0)			
185 mg (N=3)	66.7 (9 to 99)			
240 mg (N=4)	25 (1 to 81)			
275 mg (N=4)	0 (0 to 0)			

Notes:

[28] - All randomized Phase 1 participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Proportion of Participants Receiving Maintenance Therapy

End point title	Phase 2: Proportion of Participants Receiving Maintenance Therapy[29]

End point description:

Since treatment with LY2603618 was discontinued after 25 October 2012, the proportion of participants receiving maintenance therapy was not analyzed.

End point type	Secondary

End point timeframe:

Cycle 5

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for proportion of participants receiving maintenance therapy for phase 2 arms and phase 1 participants were not included.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[30]	23[31]		
Units: percentage of participants				
number (not applicable)	0	0		

Notes:

[30] - No participants analyzed due to treatment discontinuation, maintenance therapy not provided.

[31] - No participants analyzed due to treatment discontinuation, maintenance therapy not provided.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Clinical Benefit Rate: Percentage of Participant Who Achieved a Response of Stable Disease (SD), Partial Response (PR), or Complete Response (CR)

End point title	Phase 2: Clinical Benefit Rate: Percentage of Participant Who Achieved a Response of Stable Disease (SD), Partial Response (PR), or Complete Response (CR)[32]

End point description:

Clinical benefit rate is the best response CR, PR, or SD as classified by the investigators according to the RECIST, v1.1 guidelines. CR is defined as the disappearance of all target and non-target lesions, normalization of tumor marker level of non-target lesions, and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of non-target lesions or appearance of new lesions. SD is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameter since treatment started. Clinical benefit rate is calculated as a total number of participants with CR, PR, or SD divided by the total number of participants with at least 1 measurable lesion, multiplied by 100.

End point type	Secondary

End point timeframe:

Randomization until date of disease progression or death (up to 6 months after the last participant was randomized)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was for Clinical Benefit Rate for phase 2 arms and phase 1 participants were not included.

End point values	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	23[33]		
Units: percentage of participants				

number (confidence interval 90%)	69.2 (52 to 83)	47.8 (27 to 69)		

Notes:

[33] - All randomized Phase 2 participants.

Statistical analyses

Statistical analysis title	Phase 2: Clinical Benefit Rate
Comparison groups	Phase 2: Pemetrexed + Cisplatin v Phase 2: Pemetrexed + Cisplatin + LY2603618
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0946 [34]
Method	Chi-squared

Notes:

[34] - The test of treatment effect was conducted at a 2-sided alpha level of 0.10.

Secondary: Deaths

End point title	Deaths

End point description:

Deaths that occurred during the study are presented. A summary of serious and other non-serious adverse events regardless of causality is located in the Reported Adverse Events module.

End point type	Secondary

End point timeframe:

Randomization through 12 months after the last participant was randomized

End point values	Phase 1: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin + LY2603618	Phase 2: Pemetrexed + Cisplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	39[35]	23	
Units: number of participants				
Total deaths	0	21	15	
Deaths while on treatment	0	3	1	
Death within 30 days of last dose of study drug	0	1	0	
Deaths during follow-up period	0	17	14	

Notes:

[35] - All enrolled participants.

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:	
I2I-MC-JMMG	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Phase 1
Reporting group description: -	
Reporting group title	Phase 2: Pemetrexed + Cisplatin
Reporting group description: -	
Reporting group title	Phase 2: LY2603618 + Pemetrexed + Cisplatin
Reporting group description: -	

Serious adverse events	Phase 1	Phase 2: Pemetrexed + Cisplatin	Phase 2: LY2603618 + Pemetrexed + Cisplatin
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	6 / 22 (27.27%)	16 / 39 (41.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
metastases to bone			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
metastatic pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
death			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
pyrexia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pulmonary embolism			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	5 / 39 (12.82%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
respiratory failure			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
blood creatinine increased			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood urea increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
femur fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tibia fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
angina pectoris			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial fibrillation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
cerebrovascular accident			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
convulsion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ischaemic stroke			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neutropenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ileus			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vomiting			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
musculoskeletal chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
urinary tract infection bacterial			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
hyperglycaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypokalaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ketoacidosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Phase 1	Phase 2: Pemetrexed + Cisplatin	Phase 2: LY2603618 + Pemetrexed + Cisplatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	22 / 22 (100.00%)	38 / 39 (97.44%)
Vascular disorders			
circulatory collapse			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
haematoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	0 / 22 (0.00%)	4 / 39 (10.26%)
occurrences (all)	2	0	4
hypertension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	1 / 22 (4.55%)	3 / 39 (7.69%)
occurrences (all)	7	1	4
hypertensive crisis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	1	0	2
hypotension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences (all)	2	1	1
phlebitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
Surgical and medical procedures			
catheterisation venous			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	5 / 22 (22.73%)	17 / 39 (43.59%)
occurrences (all)	2	12	82
catheter site pain			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
catheter site related reaction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
catheter site swelling			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
chest discomfort			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences (all)	1	2	0
chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 22 (9.09%)	4 / 39 (10.26%)
occurrences (all)	0	3	4
chills			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	3 / 22 (13.64%)	1 / 39 (2.56%)
occurrences (all)	2	4	2
fatigue			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	13 / 14 (92.86%)	14 / 22 (63.64%)	14 / 39 (35.90%)
occurrences (all)	35	21	23
infusion site extravasation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
infusion site pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2

mucosal inflammation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	4 / 22 (18.18%)	10 / 39 (25.64%)
occurrences (all)	2	7	22
oedema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	1 / 22 (4.55%)	4 / 39 (10.26%)
occurrences (all)	3	1	7
oedema peripheral			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	3 / 22 (13.64%)	6 / 39 (15.38%)
occurrences (all)	3	3	10
pyrexia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	6 / 14 (42.86%)	9 / 22 (40.91%)	10 / 39 (25.64%)
occurrences (all)	8	10	19
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	3 / 39 (7.69%)
occurrences (all)	3	0	3
Reproductive system and breast disorders			
menstruation irregular			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[1]	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	3 / 22 (13.64%)	8 / 39 (20.51%)
occurrences (all)	4	3	19
dysphonia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 14 (0.00%)	4 / 22 (18.18%)	4 / 39 (10.26%)
occurrences (all)	0	4	4
dyspnoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	7 / 22 (31.82%)	12 / 39 (30.77%)
occurrences (all)	0	9	16
epistaxis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	5 / 39 (12.82%)
occurrences (all)	2	0	5
hiccups			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	2 / 22 (9.09%)	1 / 39 (2.56%)
occurrences (all)	5	3	1
nasal congestion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
oropharyngeal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences (all)	2	1	0
pleural effusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
productive cough			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	4 / 22 (18.18%)	0 / 39 (0.00%)
occurrences (all)	0	4	0
rhinitis allergic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences (all)	1	0	1

sneezing			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 22 (9.09%)	3 / 39 (7.69%)
occurrences (all)	0	2	3
depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences (all)	2	1	1
insomnia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 14 (35.71%)	3 / 22 (13.64%)	4 / 39 (10.26%)
occurrences (all)	6	4	5
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	3 / 39 (7.69%)
occurrences (all)	1	0	4
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	3 / 39 (7.69%)
occurrences (all)	0	0	4
blood creatinine increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	3 / 39 (7.69%)
occurrences (all)	3	1	5
blood urea increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	4 / 39 (10.26%)
occurrences (all)	0	0	4
c-reactive protein increased			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	3 / 39 (7.69%)
occurrences (all)	0	1	3
neutrophil count decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	2 / 22 (9.09%)	3 / 39 (7.69%)
occurrences (all)	6	5	4
platelet count decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	3	0	8
weight decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 22 (9.09%)	3 / 39 (7.69%)
occurrences (all)	0	3	4
white blood cell count decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences (all)	4	0	4
Injury, poisoning and procedural complications			
contrast media reaction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
infusion related reaction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	5	0	0
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	6 / 39 (15.38%)
occurrences (all)	1	1	12
dysaesthesia			
alternative dictionary used:			

MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
dysgeusia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	2 / 39 (5.13%)
occurrences (all)	2	1	2
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	2 / 22 (9.09%)	8 / 39 (20.51%)
occurrences (all)	5	2	17
hypoaesthesia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 22 (9.09%)	1 / 39 (2.56%)
occurrences (all)	0	3	1
neurotoxicity			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	7 / 39 (17.95%)
occurrences (all)	0	0	9
paraesthesia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	1 / 22 (4.55%)	4 / 39 (10.26%)
occurrences (all)	5	1	4
paresis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences (all)	1	0	1
presyncope			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences (all)	2	1	1
somnolence			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences (all)	1	0	1
tremor			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	4
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	3 / 22 (13.64%)	7 / 39 (17.95%)
occurrences (all)	16	6	16
leukocytosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 22 (9.09%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
leukopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	5 / 39 (12.82%)
occurrences (all)	2	0	11
lymphopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
neutropenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	6 / 14 (42.86%)	4 / 22 (18.18%)	8 / 39 (20.51%)
occurrences (all)	13	7	11
thrombocytopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences (all)	10	1	1
thrombocytosis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
ototoxicity			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	8 / 39 (20.51%)
occurrences (all)	0	2	22
tinnitus			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	2 / 22 (9.09%)	5 / 39 (12.82%)
occurrences (all)	4	2	7
vertigo			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	1 / 22 (4.55%)	2 / 39 (5.13%)
occurrences (all)	4	1	3
Eye disorders			
conjunctivitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	3 / 22 (13.64%)	2 / 39 (5.13%)
occurrences (all)	9	4	3
eye oedema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	3 / 39 (7.69%)
occurrences (all)	0	1	4
eyelid oedema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
lacrimation increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	2 / 39 (5.13%)
occurrences (all)	1	1	2
papilloedema			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 22 (9.09%)	2 / 39 (5.13%)
occurrences (all)	0	2	2
abdominal pain upper			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	2 / 22 (9.09%)	1 / 39 (2.56%)
occurrences (all)	3	2	1
constipation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	8 / 22 (36.36%)	18 / 39 (46.15%)
occurrences (all)	4	13	30
diarrhoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	4 / 22 (18.18%)	11 / 39 (28.21%)
occurrences (all)	5	6	17
dry mouth			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences (all)	2	0	1
dyspepsia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	2	0	2
dysphagia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences (all)	1	1	1
flatulence			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 14 (14.29%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
gastritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences (all)	1	0	1
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences (all)	2	1	1
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	12 / 14 (85.71%)	15 / 22 (68.18%)	30 / 39 (76.92%)
occurrences (all)	44	27	106
toothache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
vomiting			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	7 / 14 (50.00%)	6 / 22 (27.27%)	18 / 39 (46.15%)
occurrences (all)	13	9	42
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 14 (28.57%)	0 / 22 (0.00%)	5 / 39 (12.82%)
occurrences (all)	4	0	5
angioedema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
dermatitis acneiform			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
dry skin			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	1 / 22 (4.55%)	3 / 39 (7.69%)
occurrences (all)	2	2	3
eczema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	3 / 22 (13.64%)	2 / 39 (5.13%)
occurrences (all)	0	3	2
erythema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	2 / 39 (5.13%)
occurrences (all)	1	1	2
erythema multiforme			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences (all)	1	1	0
hyperhidrosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	1 / 22 (4.55%)	2 / 39 (5.13%)
occurrences (all)	2	1	2
nail disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
night sweats			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences (all)	1	1	0
pruritus			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	4 / 22 (18.18%)	1 / 39 (2.56%)
occurrences (all)	3	4	1

rash			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	2 / 22 (9.09%)	4 / 39 (10.26%)
occurrences (all)	3	2	4
skin discolouration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
skin disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
skin lesion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
Renal and urinary disorders			
nephrolithiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 22 (9.09%)	2 / 39 (5.13%)
occurrences (all)	1	2	3
back pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 22 (9.09%)	3 / 39 (7.69%)
occurrences (all)	1	2	3
bone pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 22 (9.09%)	3 / 39 (7.69%)
occurrences (all)	1	2	3
muscle spasms			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
musculoskeletal chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	5 / 39 (12.82%)
occurrences (all)	1	1	6
musculoskeletal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	4 / 22 (18.18%)	7 / 39 (17.95%)
occurrences (all)	3	6	11
osteoarthritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
pain in extremity			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	1 / 22 (4.55%)	3 / 39 (7.69%)
occurrences (all)	3	1	4
spinal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	4
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	2 / 22 (9.09%)	2 / 39 (5.13%)
occurrences (all)	0	2	2
candida infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
eye infection			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
gingivitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences (all)	2	1	0
herpes simplex			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
laryngitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	1 / 39 (2.56%)
occurrences (all)	1	0	2
nasopharyngitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	2 / 22 (9.09%)	5 / 39 (12.82%)
occurrences (all)	1	2	5
paronychia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
pneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
respiratory tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
rhinitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences (all)	2	1	0

upper respiratory tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 14 (21.43%)	1 / 22 (4.55%)	1 / 39 (2.56%)
occurrences (all)	3	1	1
urinary tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 22 (4.55%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	12 / 22 (54.55%)	14 / 39 (35.90%)
occurrences (all)	3	19	45
dehydration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	0 / 39 (0.00%)
occurrences (all)	1	1	0
dyslipidaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	0 / 22 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	0	0
hyperglycaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 14 (14.29%)	2 / 22 (9.09%)	1 / 39 (2.56%)
occurrences (all)	3	4	1
hypocalcaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 14 (0.00%)	0 / 22 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
hypokalaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 14 (7.14%)	1 / 22 (4.55%)	3 / 39 (7.69%)
occurrences (all)	2	1	3

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects

exposed for the reporting group. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2012	Amendment b: Incorporated pemetrexed maintenance therapy into the study design.
30 November 2012	Amendment d: As a result of the safety findings leading to the halt in enrollment, this amendment incorporated changes to the dosing regimen for participants assigned to the experimental arm.

Notes:

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.

Enrollment was halted on 25 October 2012 due to a numerical imbalance in events of thromboembolic nature between the experimental arm and the control arm.

Notes: