



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/m²) + cisplatin 75 mg/m²

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/m² + cisplatin 75 mg/m²

Day 2: LY2603618 dose from phase 1 portion of trial

After 25 Oct 2012:

Day 1: pemetrexed 500 mg/m² + cisplatin 75 mg/m²

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/m²

Day 2: LY2603618 dose determined from phase 1

After 25 Oct 2012:

Day 1: pemetrexed 500 mg/m²

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/m² + cisplatin 75 mg/m²

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/m²

| | |
|--|-------------------|
| 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/m² + cisplatin 75 mg/m²

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/m²

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 |
| 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 $75 \text{ mg}/\text{m}^2$

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 $500 \text{ mg}/\text{m}^2$ + cisplatin $75 \text{ mg}/\text{m}^2$

Day 2: LY2603618 dose from phase 1 portion of trial

After 25 Oct 2012:

Day 1: pemetrexed $500 \text{ mg}/\text{m}^2$ + cisplatin $75 \text{ mg}/\text{m}^2$

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 $500 \text{ mg}/\text{m}^2$

Day 2: LY2603618 dose determined from phase 1

After 25 Oct 2012:

Day 1: pemetrexed $500 \text{ mg}/\text{m}^2$

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 $500 \text{ mg}/\text{m}^2$ + cisplatin $75 \text{ mg}/\text{m}^2$

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 $500 \text{ mg}/\text{m}^2$

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 | | |

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 measurable 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 (\pm 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) | | | | |

| | | | | |
|----------------------|--------------|--|--|--|
| 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 occurrences (all) | 1 / 14 (7.14%) 2 | 0 / 22 (0.00%) 0 | 0 / 39 (0.00%) 0 |
| haematoma alternative dictionary used: MedDRA 16.1 | | | |
| subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 0 / 22 (0.00%) 0 | 4 / 39 (10.26%) 4 |
| hypertension alternative dictionary used: MedDRA 16.1 | | | |
| subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 7 | 1 / 22 (4.55%) 1 | 3 / 39 (7.69%) 4 |
| hypertensive crisis alternative dictionary used: MedDRA 16.1 | | | |
| subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 22 (0.00%) 0 | 2 / 39 (5.13%) 2 |
| hypotension alternative dictionary used: MedDRA 16.1 | | | |
| subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 1 / 22 (4.55%) 1 | 1 / 39 (2.56%) 1 |
| phlebitis alternative dictionary used: MedDRA 16.1 | | | |
| subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 22 (4.55%) 1 | 2 / 39 (5.13%) 2 |
| Surgical and medical procedures catheterisation venous alternative dictionary used: MedDRA 16.1 | | | |
| subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 22 (0.00%) 0 | 0 / 39 (0.00%) 0 |
| General disorders and administration site conditions asthenia alternative dictionary used: MedDRA 16.1 | | | |
| subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 5 / 22 (22.73%) 12 | 17 / 39 (43.59%) 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 occurrences (all) | 2 / 14 (14.29%) 2 | 4 / 22 (18.18%) 7 | 10 / 39 (25.64%) 22 |
| oedema alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 3 | 1 / 22 (4.55%) 1 | 4 / 39 (10.26%) 7 |
| oedema peripheral alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 3 | 3 / 22 (13.64%) 3 | 6 / 39 (15.38%) 10 |
| pyrexia alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) | 6 / 14 (42.86%) 8 | 9 / 22 (40.91%) 10 | 10 / 39 (25.64%) 19 |
| Immune system disorders hypersensitivity alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 3 | 0 / 22 (0.00%) 0 | 3 / 39 (7.69%) 3 |
| Reproductive system and breast disorders menstruation irregular alternative dictionary used: MedDRA 16.1 subjects affected / exposed ^[1] occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 8 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Respiratory, thoracic and mediastinal disorders cough alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) dysphonia alternative dictionary used: MedDRA 16.1 | 3 / 14 (21.43%) 4 | 3 / 22 (13.64%) 3 | 8 / 39 (20.51%) 19 |

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

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

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

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

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