



## Clinical trial results:

### An Open-Label Clinical Trial of MORAb-009 in Combination With Pemetrexed and Cisplatin in Subjects With Mesothelioma

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2008-005448-18  |
| Trial protocol           | DE ES NL        |
| Global end of trial date | 10 January 2014 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 01 May 2016  |
| First version publication date | 01 May 2016  |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | MORAb-009-003 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00738582 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Morphotek (subsidiary of Eisai)                  |
| Sponsor organisation address | 210 Welsh Pool Road, Exton, United States, 19341 |
| Public contact               | Eisai Call Center, Eisai Inc., 888 422-4743,     |
| Scientific contact           | Eisai Call Center, Eisai Inc., 888 422-4743,     |

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                       | 23 July 2014    |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 01 June 2011    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 10 January 2014 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To determine the effect on progression-free survival (PFS) of adding amatuximab (MORAb-009) to the combination of pemetrexed and cisplatin in the treatment of subjects with unresectable malignant pleural mesothelioma (MPM) who have not received prior systemic therapy, as assessed using the modified Response Evaluation Criteria in Solid Tumors (RECIST) for the assessment of response in MPM. Secondary:

- To evaluate antitumor activity, as assessed by objective tumor response (overall response rate [ORR])
- To evaluate duration of response (DR)
- To evaluate overall survival (OS)
- To determine the safety and tolerability of amatuximab when administered with pemetrexed and cisplatin

Exploratory (various tests were performed)

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312 (2013)
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy:

Pemetrexed and cisplatin were administered as standard of care according to the approved labeled use of the products for treatment of MPM in each country.

Evidence for comparator:

Not applicable

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 11 February 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | Spain: 13      |
| Country: Number of subjects enrolled | Germany: 28    |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 39 |
| Country: Number of subjects enrolled | Canada: 3         |
| Worldwide total number of subjects   | 89                |
| EEA total number of subjects         | 47                |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                 | 31 |
| Adults (18-64 years)                      | 58 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All screening procedures were to be completed within 30 days before and including the Cycle 1 Day 1 visit. Scheduling of the first infusions of pemetrexed and cisplatin was done to accommodate timing of pretreatments, as defined in the approved, country-specific drug package inserts.

### Period 1

|                              |                     |
|------------------------------|---------------------|
| Period 1 title               | Combination Therapy |
| Is this the baseline period? | Yes                 |
| Allocation method            | Not applicable      |
| Blinding used                | Not blinded         |

### Arms

|           |                                 |
|-----------|---------------------------------|
| Arm title | Amatuximab/Pemetrexed/Cisplatin |
|-----------|---------------------------------|

Arm description:

During the treatment period, participants received up to 6 cycles of combination therapy with amatuximab, pemetrexed and cisplatin. Participants who completed combination therapy or who discontinued chemotherapy because of intolerable toxicity continued receiving single agent amatuximab (maintenance therapy) for all subsequent cycles until disease progression occurred.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Amatuximab            |
| Investigational medicinal product code |                       |
| Other name                             | MORAb-009             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Amatuximab 5 mg/kg by intravenous (IV) infusion in 0.9% normal saline; administered on Day 1 and Day 8 of each 21 day cycle for up to 6 cycles or until disease progression was identified, whichever occurred first.

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | Pemetrexed                      |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Pemetrexed 500 mg/m<sup>2</sup> by IV infusion in 0.9% normal saline over approximately 10 minutes; administered on Day 1 of each 21-day cycle for up to 6 cycles or until disease progression was identified, whichever occurred first.

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | Cisplatin                       |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection/infusion |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Cisplatin 75 mg/m<sup>2</sup> by IV infusion in 0.9% normal saline over approximately 2 hours; administered on Day 1 of each 21-day cycle for up to 6 cycles or until disease progression was identified, whichever occurred first.

| Number of subjects in period 1 | Amatuximab/Pemetrexed/Cisplatin |
|--------------------------------|---------------------------------|
| Started                        | 89                              |
| Completed                      | 56                              |
| Not completed                  | 33                              |
| Adverse event, serious fatal   | 4                               |
| Physician decision             | 1                               |
| Adverse event, non-fatal       | 12                              |
| Toxicity to Chemotherapy       | 1                               |
| Progressive Disease            | 9                               |
| Not specified                  | 5                               |
| Completed Combination Therapy  | 1                               |

## Period 2

|                              |                     |
|------------------------------|---------------------|
| Period 2 title               | Maintenance Therapy |
| Is this the baseline period? | No                  |
| Allocation method            | Not applicable      |
| Blinding used                | Not blinded         |

## Arms

|           |            |
|-----------|------------|
| Arm title | Amatuximab |
|-----------|------------|

### Arm description:

Treatment with amatuximab (5 mg/kg) was administered on Days 1 and 8 of each 21-day cycle and continued until disease progression occurred.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Amatuximab            |
| Investigational medicinal product code |                       |
| Other name                             | MORAb-009             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

### Dosage and administration details:

Amatuximab 5 mg/kg by intravenous (IV) infusion in 0.9% normal saline; administered on Day 1 and Day 8 of each 21 day cycle until disease progression.

| Number of subjects in period 2 | Amatuximab |
|--------------------------------|------------|
| Started                        | 56         |
| Completed                      | 0          |
| Not completed                  | 56         |
| Consent withdrawn by subject   | 1          |
| Adverse event, non-fatal       | 6          |

|                     |    |
|---------------------|----|
| Progressive Disease | 47 |
| Not specified       | 2  |

## Baseline characteristics

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Amatuximab/Pemetrexed/Cisplatin |
|-----------------------|---------------------------------|

Reporting group description:

During the treatment period, participants received up to 6 cycles of combination therapy with amatuximab, pemetrexed and cisplatin. Participants who completed combination therapy or who discontinued chemotherapy because of intolerable toxicity continued receiving single agent amatuximab (maintenance therapy) for all subsequent cycles until disease progression occurred.

| Reporting group values             | Amatuximab/Pemetrexed/Cisplatin | Total |  |
|------------------------------------|---------------------------------|-------|--|
| Number of subjects                 | 89                              | 89    |  |
| Age categorical<br>Units: Subjects |                                 |       |  |

|  |                |    |  |
|--|----------------|----|--|
| Age continuous<br>Units: years<br>median<br>full range (min-max) | 67<br>46 to 80 | -  |  |
| Gender categorical<br>Units: Subjects                            |                |    |  |
| Female   | 20             | 20 |  |
| Male   | 69             | 69 |  |

## End points

### End points reporting groups

|   |                                 |
|---|---------------------------------|
| Reporting group title   | Amatuximab/Pemetrexed/Cisplatin |
| Reporting group description:<br>During the treatment period, participants received up to 6 cycles of combination therapy with amatuximab, pemetrexed and cisplatin. Participants who completed combination therapy or who discontinued chemotherapy because of intolerable toxicity continued receiving single agent amatuximab (maintenance therapy) for all subsequent cycles until disease progression occurred. |                                 |
| Reporting group title   | Amatuximab                      |
| Reporting group description:<br>Treatment with amatuximab (5 mg/kg) was administered on Days 1 and 8 of each 21-day cycle and continued until disease progression occurred.   |                                 |
| Subject analysis set title  | Amatuximab (PFS Responders)     |
| Subject analysis set type   | Sub-group analysis              |
| Subject analysis set description:<br>Subject analysis set used as comparison group (PFS Responders) in statistical data used for progression-free survival.   |                                 |
| Subject analysis set title  | Amatuximab (PFS Non-Responders) |
| Subject analysis set type   | Sub-group analysis              |
| Subject analysis set description:<br>Subject analysis set used as comparison group (PFS Non-Responders) in statistical data used for progression-free survival.   |                                 |

### Primary: Progression Free Survival at Month 6

|   |                                      |
|---|--------------------------------------|
| End point title   | Progression Free Survival at Month 6 |
| End point description:<br>PFS was defined as the time from the date of the first dose of amatuximab to the date of disease progression or death due to any cause, as determined by independent radiologist based on the modified RECIST utilizing the total tumor measurement (performed by computerized tomography (CT)/ magnetic resonance imaging (MRI)) which includes the pleural unidimensional measure plus the total of the target lesion(s) measurement (Byrne and Nowak, 2004). A "response", in terms of PFS, was defined to be at least a 6-month stabilization of disease. The data is presented as number of participants (PFS responders and non-responders) at 6 months for the first 77 participants enrolled. Progressive disease (PD) as measured by Modified RECIST was defined as an increase of at least 20% in the total tumor measurement over the nadir measurement, or the appearance of one or more new lesions. |                                      |
| End point type  | Primary                              |
| End point timeframe:<br>Month 6   |                                      |

| End point values            | Amatuximab (PFS Responders) | Amatuximab (PFS Non-Responders) |  |  |
|-----------------------------|-----------------------------|---------------------------------|--|--|
| Subject group type          | Subject analysis set        | Subject analysis set            |  |  |
| Number of subjects analysed | 26                          | 51                              |  |  |
| Units: Participants         |                             |                                 |  |  |
| number (not applicable)     | 26                          | 51                              |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Confidence Interval   |
| Comparison groups                       | Amatuximab (PFS Responders) v Amatuximab (PFS Non-Responders) |
| Number of subjects included in analysis | 77  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Clopper-Pearson   |
| Point estimate                          | 33.8  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 23.4  |
| upper limit                             | 45.4  |

### Secondary: Overall Response Rate (ORR)

|  |                             |
|--|-----------------------------|
| End point title  | Overall Response Rate (ORR) |
| End point description:   |                             |
| ORR, defined as the percentage of participants with objective evidence of complete response (CR) or partial response (PR) as determined by independent radiologist based on the modified RECIST utilizing the total tumor measurement (performed by CT/ MRI) which includes the pleural unidimensional measure plus the total of the target lesion(s) measurement (Byrne and Nowak, 2004). Tumor assessments performed up to the initiation of further anticancer therapy were considered. CR was defined as the disappearance of all target lesions with no evidence of tumor elsewhere, and PR was defined as at least a 30% reduction in the total tumor measurement. A confirmed response required a repeat observation on two occasions 4 weeks apart. ORR = CR + PR. There was no subject with CR. |                             |
| End point type   | Secondary                   |
| End point timeframe:   |                             |
| From the date of first dose until evidence of complete response (CR) or partial response (PR), up to approximately 5 years.  |                             |

|                                   |                                 |  |  |  |
|-----------------------------------|---------------------------------|--|--|--|
| <b>End point values</b>           | Amatuximab/Pemetrexed/Cisplatin |  |  |  |
| Subject group type                | Reporting group                 |  |  |  |
| Number of subjects analysed       | 84                              |  |  |  |
| Units: Percentage of Participants |                                 |  |  |  |
| number (not applicable)           | 34.5                            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DR)

|   |                           |
|---|---------------------------|
| End point title   | Duration of Response (DR) |
| End point description:  |                           |
| DR was derived for those participants who achieved a PFS Response and had an objective evidence of CR or PR. DR was defined as the time (in months) from first documentation of objective response (CR or |                           |

PR) to the first documentation of disease progression [as determined by independent radiologist based on the modified RECIST utilizing the total tumor measurement (performed by CT/ MRI) which includes the pleural unidimensional measure plus the total of the target lesion(s) measurement (Byrne and Nowak, 2004)]. Tumor assessments performed up to the initiation of further anticancer therapy were considered.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the first documentation of objective response (CR or PR) to the first documentation of disease progression, up to approximately 5 years.

|                                  |   |  |  |  |
|----------------------------------|---|--|--|--|
| <b>End point values</b>          | Amatuximab/P<br>emetrexed/Cis<br>platin |  |  |  |
| Subject group type               | Reporting group                         |  |  |  |
| Number of subjects analysed      | 29                                      |  |  |  |
| Units: Months                    |   |  |  |  |
| median (confidence interval 95%) | 9.2 (6 to 16.2)                         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Tumor Response (TTR)

|                 |                              |
|-----------------|------------------------------|
| End point title | Time to Tumor Response (TTR) |
|-----------------|------------------------------|

End point description:

TTR was derived for those participants with objective evidence of CR or PR. TTR was defined as the time from the date of the first dose of amatuximab to first documentation of objective tumor response.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of the first dose to first documentation of objective response, up to approximately 5 years.

|                                  |   |  |  |  |
|----------------------------------|---|--|--|--|
| <b>End point values</b>          | Amatuximab/P<br>emetrexed/Cis<br>platin |  |  |  |
| Subject group type               | Reporting group                         |  |  |  |
| Number of subjects analysed      | 29                                      |  |  |  |
| Units: Months                    |   |  |  |  |
| median (confidence interval 95%) | 2.3 (2.1 to 3.8)                        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from the date of the first dose of amatuximab to the date of death.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of first dose to the date of death, up to approximately 5 years.

| End point values                 | Amatuximab/P<br>emetrexed/Cis<br>platin |  |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Reporting group                         |  |  |  |
| Number of subjects analysed      | 89                                      |  |  |  |
| Units: Months                    |   |  |  |  |
| median (confidence interval 95%) | 14.8 (12.4 to<br>18.8)                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Progression Free Survival

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Overall Progression Free Survival |
|-----------------|-----------------------------------|

End point description:

Overall PFS was defined as the time from the date of first dose of amatuximab to the date of disease progression or death due to any cause. In the absence of confirmation of death, the survival time was censored at the date of the last follow-up contact. Tumor assessments performed up to the initiation of further anticancer therapy were considered.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of first dose of amatuximab to the date of disease progression, up to approximately 5 years.

| End point values                 | Amatuximab/P<br>emetrexed/Cis<br>platin |  |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Reporting group                         |  |  |  |
| Number of subjects analysed      | 84                                      |  |  |  |
| Units: Months                    |   |  |  |  |
| median (confidence interval 95%) | 6.3 (6 to 7.8)                          |  |  |  |

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For each participant, from the first dose till 30 days after the last dose or up to approximately 5 years

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs), defined as an AE that started/increased in severity on/after the first dose of study drug up to 30 days after final dose of study drug. Per the study Statistical Analysis Plan (SAS), the TEAEs presented include serious and non-serious TEAEs. Additionally, serious TEAEs are presented separately.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Amatuximab/Pemetrexed/Cisplatin |
|-----------------------|---------------------------------|

Reporting group description: -

| Serious adverse events  | Amatuximab/Pemetrexed/Cisplatin |  |  |
|---|---------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                 |  |  |
| subjects affected / exposed   | 48 / 89 (53.93%)                |  |  |
| number of deaths (all causes)                                       | 76                              |  |  |
| number of deaths resulting from adverse events                      |                                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                 |  |  |
| Tumour pain   |                                 |  |  |
| subjects affected / exposed   | 1 / 89 (1.12%)                  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                           |  |  |
| deaths causally related to treatment / all                          | 0 / 0                           |  |  |
| Vascular disorders  |                                 |  |  |
| Embolism  |                                 |  |  |
| subjects affected / exposed   | 1 / 89 (1.12%)                  |  |  |
| occurrences causally related to treatment / all                     | 1 / 1                           |  |  |
| deaths causally related to treatment / all                          | 0 / 0                           |  |  |
| Hypertension  |                                 |  |  |
| subjects affected / exposed   | 1 / 89 (1.12%)                  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                           |  |  |
| deaths causally related to treatment / all                          | 0 / 0                           |  |  |
| Peripheral embolism   |                                 |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Thrombosis   |                |  |  |
| subjects affected / exposed                          | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Fatigue  |                |  |  |
| subjects affected / exposed                          | 3 / 89 (3.37%) |  |  |
| occurrences causally related to treatment / all      | 1 / 3          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Non-cardiac chest pain                               |                |  |  |
| subjects affected / exposed                          | 3 / 89 (3.37%) |  |  |
| occurrences causally related to treatment / all      | 1 / 4          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pyrexia  |                |  |  |
| subjects affected / exposed                          | 3 / 89 (3.37%) |  |  |
| occurrences causally related to treatment / all      | 1 / 3          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Asthenia   |                |  |  |
| subjects affected / exposed                          | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Chills   |                |  |  |
| subjects affected / exposed                          | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Immune system disorders                              |                |  |  |
| Hypersensitivity                                     |                |  |  |
| subjects affected / exposed                          | 4 / 89 (4.49%) |  |  |
| occurrences causally related to treatment / all      | 4 / 5          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Drug hypersensitivity                           |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Reproductive system and breast disorders        |                |  |  |
| Prostatitis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 4 / 89 (4.49%) |  |  |
| occurrences causally related to treatment / all | 0 / 5          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumothorax                                    |                |  |  |
| subjects affected / exposed                     | 2 / 89 (2.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Acute respiratory distress syndrome             |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Epistaxis                                       |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 1 / 1          |  |  |
| Psychiatric disorders                           |                |  |  |
| Confusional state                               |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| C-reactive protein increased                    |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| International normalised ratio increased        |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Neutrophil count decreased                      |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Platelet count decreased                        |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| White blood cell count decreased                |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Cystitis radiation                              |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infusion related reaction                       |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Seroma  |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Spinal compression fracture                     |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Toxicity to various agents                      |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Atrial fibrillation                             |                |  |  |
| subjects affected / exposed                     | 5 / 89 (5.62%) |  |  |
| occurrences causally related to treatment / all | 1 / 6          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Angina pectoris                                 |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardio-respiratory arrest                       |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pericarditis                                    |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tachyarrhythmia                                 |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ventricular fibrillation                        |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Syncope   |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Transient ischaemic attack                      |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Neutropenia                                     |                |  |  |
| subjects affected / exposed                     | 5 / 89 (5.62%) |  |  |
| occurrences causally related to treatment / all | 1 / 5          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Anaemia   |                |  |  |
| subjects affected / exposed                     | 3 / 89 (3.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ear and labyrinth disorders                     |                |  |  |
| Vertigo   |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Gastrointestinal disorders                      |                |  |  |
| Ascites   |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ileus paralytic                                 |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea  |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Stomatitis                                      |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Hyperbilirubinaemia                             |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Calculus urinary                                |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal failure acute                             |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal impairment                                |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Intervertebral disc protrusion                  |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Muscle spasms                                   |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 2 / 89 (2.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Appendicitis                                    |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Device related infection                        |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Infectious peritonitis                          |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Neutropenic sepsis                              |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pyopneumothorax                                 |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory tract infection                     |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urosepsis                                       |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Hyponatraemia                                   |                |  |  |
| subjects affected / exposed                     | 3 / 89 (3.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 2 / 89 (2.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyperglycaemia                                  |                |  |  |
| subjects affected / exposed                     | 1 / 89 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Amatuximab/Pemetrexed/Cisplatin |  |  |
|---|---------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                 |  |  |
| subjects affected / exposed                           | 89 / 89 (100.00%)               |  |  |
| Vascular disorders                                    |                                 |  |  |
| Hypertension  |                                 |  |  |
| subjects affected / exposed                           | 10 / 89 (11.24%)                |  |  |
| occurrences (all)                                     | 13                              |  |  |
| Hypotension   |                                 |  |  |
| subjects affected / exposed                           | 5 / 89 (5.62%)                  |  |  |
| occurrences (all)                                     | 6                               |  |  |
| General disorders and administration site conditions  |                                 |  |  |
| Fatigue   |                                 |  |  |
| subjects affected / exposed                           | 56 / 89 (62.92%)                |  |  |
| occurrences (all)                                     | 87                              |  |  |
| Non-cardiac chest pain                                |                                 |  |  |
| subjects affected / exposed                           | 26 / 89 (29.21%)                |  |  |
| occurrences (all)                                     | 34                              |  |  |
| Asthenia  |                                 |  |  |
| subjects affected / exposed                           | 19 / 89 (21.35%)                |  |  |
| occurrences (all)                                     | 40                              |  |  |
| Oedema peripheral                                     |                                 |  |  |
| subjects affected / exposed                           | 19 / 89 (21.35%)                |  |  |
| occurrences (all)                                     | 25                              |  |  |
| Chills  |                                 |  |  |
| subjects affected / exposed                           | 17 / 89 (19.10%)                |  |  |
| occurrences (all)                                     | 37                              |  |  |
| Pyrexia   |                                 |  |  |
| subjects affected / exposed                           | 16 / 89 (17.98%)                |  |  |
| occurrences (all)                                     | 17                              |  |  |
| Mucosal inflammation                                  |                                 |  |  |
| subjects affected / exposed                           | 6 / 89 (6.74%)                  |  |  |
| occurrences (all)                                     | 8                               |  |  |
| Chest discomfort                                      |                                 |  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 5 / 89 (5.62%)<br>6  |  |  |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)   | 12 / 89 (13.48%)<br>24   |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Hiccups<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Pleuritic pain<br>subjects affected / exposed<br>occurrences (all) | 28 / 89 (31.46%)<br>43<br><br>21 / 89 (23.60%)<br>26<br><br>12 / 89 (13.48%)<br>21<br><br>9 / 89 (10.11%)<br>9<br><br>8 / 89 (8.99%)<br>10<br><br>5 / 89 (5.62%)<br>5<br><br>5 / 89 (5.62%)<br>6 |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 9 / 89 (10.11%)<br>9   |  |  |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)  | 20 / 89 (22.47%)<br>21   |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)  | 14 / 89 (15.73%)<br>22 |  |  |
| Breath sounds abnormal<br>subjects affected / exposed<br>occurrences (all)  | 6 / 89 (6.74%)<br>6    |  |  |
| Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)   | 6 / 89 (6.74%)<br>7    |  |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)  | 5 / 89 (5.62%)<br>9    |  |  |
| Injury, poisoning and procedural complications<br>Infusion related reaction<br>subjects affected / exposed<br>occurrences (all) | 7 / 89 (7.87%)<br>22   |  |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 8 / 89 (8.99%)<br>11   |  |  |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)   | 7 / 89 (7.87%)<br>10   |  |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)  | 5 / 89 (5.62%)<br>5    |  |  |
| Nervous system disorders<br>Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                       | 19 / 89 (21.35%)<br>21 |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 17 / 89 (19.10%)<br>21 |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 16 / 89 (17.98%)<br>19 |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 12 / 89 (13.48%)<br>16 |  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)          | 10 / 89 (11.24%)<br>12 |  |  |
| Polyneuropathy<br>subjects affected / exposed<br>occurrences (all)        | 6 / 89 (6.74%)<br>6    |  |  |
| Blood and lymphatic system disorders                                      |                        |  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)               | 27 / 89 (30.34%)<br>40 |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)           | 26 / 89 (29.21%)<br>47 |  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)            | 10 / 89 (11.24%)<br>23 |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)      | 5 / 89 (5.62%)<br>5    |  |  |
| Ear and labyrinth disorders   |                        |  |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)              | 12 / 89 (13.48%)<br>17 |  |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)               | 7 / 89 (7.87%)<br>9    |  |  |
| Eye disorders   |                        |  |  |
| Lacrimation increased<br>subjects affected / exposed<br>occurrences (all) | 10 / 89 (11.24%)<br>10 |  |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)        | 5 / 89 (5.62%)<br>5    |  |  |
| Gastrointestinal disorders  |                        |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| Nausea                                 |                  |  |  |
| subjects affected / exposed            | 66 / 89 (74.16%) |  |  |
| occurrences (all)                      | 143              |  |  |
| Constipation                           |                  |  |  |
| subjects affected / exposed            | 32 / 89 (35.96%) |  |  |
| occurrences (all)                      | 41               |  |  |
| Vomiting                               |                  |  |  |
| subjects affected / exposed            | 31 / 89 (34.83%) |  |  |
| occurrences (all)                      | 55               |  |  |
| Diarrhoea                              |                  |  |  |
| subjects affected / exposed            | 27 / 89 (30.34%) |  |  |
| occurrences (all)                      | 33               |  |  |
| Abdominal pain upper                   |                  |  |  |
| subjects affected / exposed            | 15 / 89 (16.85%) |  |  |
| occurrences (all)                      | 19               |  |  |
| Stomatitis                             |                  |  |  |
| subjects affected / exposed            | 13 / 89 (14.61%) |  |  |
| occurrences (all)                      | 15               |  |  |
| Dyspepsia                              |                  |  |  |
| subjects affected / exposed            | 11 / 89 (12.36%) |  |  |
| occurrences (all)                      | 12               |  |  |
| Abdominal discomfort                   |                  |  |  |
| subjects affected / exposed            | 8 / 89 (8.99%)   |  |  |
| occurrences (all)                      | 8                |  |  |
| Abdominal pain                         |                  |  |  |
| subjects affected / exposed            | 7 / 89 (7.87%)   |  |  |
| occurrences (all)                      | 8                |  |  |
| Abdominal distension                   |                  |  |  |
| subjects affected / exposed            | 6 / 89 (6.74%)   |  |  |
| occurrences (all)                      | 7                |  |  |
| Flatulence                             |                  |  |  |
| subjects affected / exposed            | 5 / 89 (5.62%)   |  |  |
| occurrences (all)                      | 5                |  |  |
| Skin and subcutaneous tissue disorders |                  |  |  |
| Rash                                   |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 16 / 89 (17.98%) |  |  |
| occurrences (all)                               | 20               |  |  |
| Alopecia  |                  |  |  |
| subjects affected / exposed                     | 11 / 89 (12.36%) |  |  |
| occurrences (all)                               | 12               |  |  |
| Pruritus  |                  |  |  |
| subjects affected / exposed                     | 11 / 89 (12.36%) |  |  |
| occurrences (all)                               | 12               |  |  |
| Dry skin  |                  |  |  |
| subjects affected / exposed                     | 9 / 89 (10.11%)  |  |  |
| occurrences (all)                               | 11               |  |  |
| Night sweats                                    |                  |  |  |
| subjects affected / exposed                     | 7 / 89 (7.87%)   |  |  |
| occurrences (all)                               | 7                |  |  |
| Erythema  |                  |  |  |
| subjects affected / exposed                     | 5 / 89 (5.62%)   |  |  |
| occurrences (all)                               | 13               |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Back pain                                       |                  |  |  |
| subjects affected / exposed                     | 19 / 89 (21.35%) |  |  |
| occurrences (all)                               | 27               |  |  |
| Arthralgia                                      |                  |  |  |
| subjects affected / exposed                     | 9 / 89 (10.11%)  |  |  |
| occurrences (all)                               | 12               |  |  |
| Musculoskeletal chest pain                      |                  |  |  |
| subjects affected / exposed                     | 9 / 89 (10.11%)  |  |  |
| occurrences (all)                               | 11               |  |  |
| Pain in extremity                               |                  |  |  |
| subjects affected / exposed                     | 9 / 89 (10.11%)  |  |  |
| occurrences (all)                               | 11               |  |  |
| Flank pain                                      |                  |  |  |
| subjects affected / exposed                     | 8 / 89 (8.99%)   |  |  |
| occurrences (all)                               | 12               |  |  |
| Musculoskeletal pain                            |                  |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 8 / 89 (8.99%)   |  |  |
| occurrences (all)                  | 9                |  |  |
| Muscle spasms                      |                  |  |  |
| subjects affected / exposed        | 6 / 89 (6.74%)   |  |  |
| occurrences (all)                  | 10               |  |  |
| Myalgia                            |                  |  |  |
| subjects affected / exposed        | 5 / 89 (5.62%)   |  |  |
| occurrences (all)                  | 5                |  |  |
| Infections and infestations        |                  |  |  |
| Nasopharyngitis                    |                  |  |  |
| subjects affected / exposed        | 13 / 89 (14.61%) |  |  |
| occurrences (all)                  | 19               |  |  |
| Urinary tract infection            |                  |  |  |
| subjects affected / exposed        | 7 / 89 (7.87%)   |  |  |
| occurrences (all)                  | 10               |  |  |
| Pneumonia                          |                  |  |  |
| subjects affected / exposed        | 5 / 89 (5.62%)   |  |  |
| occurrences (all)                  | 5                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Decreased appetite                 |                  |  |  |
| subjects affected / exposed        | 43 / 89 (48.31%) |  |  |
| occurrences (all)                  | 65               |  |  |
| Hypomagnesaemia                    |                  |  |  |
| subjects affected / exposed        | 10 / 89 (11.24%) |  |  |
| occurrences (all)                  | 22               |  |  |
| Hyponatraemia                      |                  |  |  |
| subjects affected / exposed        | 9 / 89 (10.11%)  |  |  |
| occurrences (all)                  | 11               |  |  |
| Dehydration                        |                  |  |  |
| subjects affected / exposed        | 6 / 89 (6.74%)   |  |  |
| occurrences (all)                  | 7                |  |  |
| Hyperkalaemia                      |                  |  |  |
| subjects affected / exposed        | 6 / 89 (6.74%)   |  |  |
| occurrences (all)                  | 6                |  |  |
| Hypokalaemia                       |                  |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 5 / 89 (5.62%) |  |  |
| occurrences (all)           | 7              |  |  |
| Hyperglycaemia              |                |  |  |
| subjects affected / exposed | 5 / 89 (5.62%) |  |  |
| occurrences (all)           | 6              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 24 June 2009     | <ul style="list-style-type: none"><li>- The number of sites was increased 25 to 35</li><li>- An IDMC review of safety after 8 subjects completed one cycle of combination therapy was added</li><li>- Added to inclusion criterion #3 "...or who are otherwise not candidates for curative surgery"</li><li>- Removed from inclusion criterion #3 the requirement of 75% sarcomatous content</li><li>- Amended inclusion criterion #9 to instruct subjects to maintain adequate birth control throughout the study and for at least 8 weeks (5 half-lives) after the last dose of amatuximab</li><li>- Removed exclusion criterion #11 which required contrast agent for tumor imaging and clarified in procedures that use of contrast agent with CT was recommended</li><li>- Reduced the number of cycles on combination therapy from 12 to 6</li><li>- Removed the requirement for use of non-protein binding tubing for study drug infusions</li><li>- Specified that amatuximab premedications be administered approximately one half hour before the infusion</li><li>- Removed references to oral administration of diphenhydramine to allow standard practice per site</li><li>- Specified that pemetrexed and cisplatin (and associated premedications) should be administered per package insert or per the site's standard practice</li><li>- Removed the requirement to collect source and length of exposure to asbestos</li><li>- Clarified timing of vital signs assessment as 1, 2, and 4 hours post amatuximab infusion, not following infusion of pemetrexed and cisplatin</li><li>- Removed the requirement for imaging of the pelvis</li><li>- Moved baseline PFT assessment to Screening visit</li><li>- Expanded the definition of Overall PFS to differentiate it from the primary endpoint</li></ul> |
| 19 November 2010 | <ul style="list-style-type: none"><li>- Added US Adopted Name for MORAb-009 (amatuximab)</li><li>- Removed exploratory fludeoxyglucose and single-photon emission CT imaging substudies</li><li>- Clarified the time point for the interim analysis and corresponding IDMC review meeting as "33 subjects evaluable for PFS at 6 months" instead of "33 subjects have completed the first enrollment stage."</li><li>- Made the following modifications to the Inclusion criteria:<ul style="list-style-type: none"><li>&gt; Clarified requirements for measurable disease at screening as "measurable disease at Screening using CT-scans covering chest/thorax and abdomen" in criterion no. 4</li><li>&gt; Specified details of surgical eligibility related to criterion no. 3</li><li>&gt; Specified diagnosis of pleural mesothelioma in criterion no. 3</li></ul></li><li>- Made the following modifications to the Exclusion criteria:<ul style="list-style-type: none"><li>&gt; Clarified the specific exclusion of peritoneal mesothelioma in criterion no. 1</li><li>&gt; Added an allowance for prior use of low-dose corticosteroids to criterion no. 9</li></ul></li><li>- Specified "pleural" mesothelioma in inclusion and exclusion criteria</li><li>- Added request for delivery of imaging data after discontinuation due to either intolerance to study treatment or any reason other than unequivocal disease progression</li><li>- Revised to state that interim analysis decision to complete Stage 2 of Simon 2-stage design would be determined by the IDMC based on the primary statistical assessment of PFS response using independent radiologist imaging assessments rather than the investigator's imaging assessment of tumor response</li></ul>  |

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|-----------------|---|
| 16 May 2011     | <ul style="list-style-type: none"> <li>- Changed time frame for concomitant medication data collection to 30 days prior to first dose through 30 days after the last dose of amatuximab</li> <li>- Clarified temperature monitoring log for amatuximab</li> <li>- Extensively clarified reporting of Grade 3 versus Grade 4 AEs</li> <li>- Clarified pregnancy reporting</li> <li>- Updated ADA blood draw schedule for single-agent maintenance therapy as Week 1 of every third cycle</li> <li>- Updated single-agent blood draw schedule and amount of blood to be collected</li> <li>- Updated instructions for NCI CTCAE Grade 3 or 4 Allergy Mandated IRB/IEC notification of deviations from the protocol or SAEs as "must" rather than "should" notify and updating of study status if "required" rather than "requested"</li> <li>- Included both references to Federal Code of Regulations and ICH Guidelines in regards to the inclusion of the elements of an informed consent form</li> <li>- Clarified subject confidentiality</li> <li>- Clarification of data management plan, eCRF details and study materials</li> <li>- Clarified the instructions and regulations for required retention of data</li> </ul> |
| 03 October 2011 | Increased time frame for subject treatment to 84 months and follow-up to 30 months  |
| 14 June 2012    | Implemented an exploratory endpoint of tissue-based biomarkers as a surrogate for predicting response to immunotherapy  |

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.

Results were ready but could not be released before 21 July 2015 due to EudraCT System issues.

Notes: