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 case 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:

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)	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/m2 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/m2 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			
Units: Subjects			
Age continuous			
Units: years			
median	67		
full range (min-max)	46 to 80	-	
Gender categorical			
Units: Subjects			
Female	20	20	
Male	69	69	

End points

End points 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 title	Amatuximab
Reporting group 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.	
Subject analysis set title	Amatuximab (PFS Responders)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
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:	
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:	
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:	
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: Partcipants				
number (not applicable)	26	51		

Statistical analyses

Statistical analysis title	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.

End point values	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.

End point values	Amatuximab/Pemetrexed/Cisplatin			
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.

End point values	Amatuximab/Pemetrexed/Cisplatin			
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/Pemetrexed/Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	89			
Units: Months				
median (confidence interval 95%)	14.8 (12.4 to 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/Pemetrexed/Cisplatin			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Months				
median (confidence interval 95%)	6.3 (6 to 7.8)			

Statistical analyses

No statistical analyses for this end point

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 %

Non-serious adverse events	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 inflamation			
subjects affected / exposed	6 / 89 (6.74%)		
occurrences (all)	8		
Chest discomfort			

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

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

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

Nausea subjects affected / exposed occurrences (all)	66 / 89 (74.16%) 143		
Constipation subjects affected / exposed occurrences (all)	32 / 89 (35.96%) 41		
Vomiting subjects affected / exposed occurrences (all)	31 / 89 (34.83%) 55		
Diarrhoea subjects affected / exposed occurrences (all)	27 / 89 (30.34%) 33		
Abdominal pain upper subjects affected / exposed occurrences (all)	15 / 89 (16.85%) 19		
Stomatitis subjects affected / exposed occurrences (all)	13 / 89 (14.61%) 15		
Dyspepsia subjects affected / exposed occurrences (all)	11 / 89 (12.36%) 12		
Abdominal discomfort subjects affected / exposed occurrences (all)	8 / 89 (8.99%) 8		
Abdominal pain subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 8		
Abdominal distension subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 7		
Flatulence subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 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		
Muskuloskeletal 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		
Hyperglycaemmia			
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	- The number of sites was increased 25 to 35 - An IDMC review of safety after 8 subjects completed one cycle of combination therapy was added - Added to inclusion criterion #3 "...or who are otherwise not candidates for curative surgery" - Removed from inclusion criterion #3 the requirement of 75% sarcomatous content - 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 - Removed exclusion criterion #11 which required contrast agent for tumor imaging and clarified in procedures that use of contrast agent with CT was recommended - Reduced the number of cycles on combination therapy from 12 to 6 - Removed the requirement for use of non-protein binding tubing for study drug infusions - Specified that amatuximab premedications be administered approximately one half hour before the infusion - Removed references to oral administration of diphenhydramine to allow standard practice per site - Specified that pemetrexed and cisplatin (and associated premedications) should be administered per package insert or per the site's standard practice - Removed the requirement to collect source and length of exposure to asbestos - Clarified timing of vital signs assessment as 1, 2, and 4 hours post amatuximab infusion, not following infusion of pemetrexed and cisplatin - Removed the requirement for imaging of the pelvis - Moved baseline PFT assessment to Screening visit - Expanded the definition of Overall PFS to differentiate it from the primary endpoint
19 November 2010	- Added US Adopted Name for MORAb-009 (amatuximab) - Removed exploratory fludeoxyglucose and single-photon emission CT imaging substudies - 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." - Made the following modifications to the Inclusion criteria: >Clarified requirements for measurable disease at screening as "measurable disease at Screening using CT-scans covering chest/thorax and abdomen" in criterion no. 4 > Specified details of surgical eligibility related to criterion no. 3 > Specified diagnosis of pleural mesothelioma in criterion no. 3 - Made the following modifications to the Exclusion criteria: >Clarified the specific exclusion of peritoneal mesothelioma in criterion no. 1 >Added an allowance for prior use of low-dose corticosteroids to criterion no. 9 - Specified “pleural” mesothelioma in inclusion and exclusion criteria - Added request for delivery of imaging data after discontinuation due to either intolerance to study treatment or any reason other than unequivocal disease progression - 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

16 May 2011	- Changed time frame for concomitant medication data collection to 30 days prior to first dose through 30 days after the last dose of amatuximab - Clarified temperature monitoring log for amatuximab - Extensively clarified reporting of Grade 3 versus Grade 4 AEIs - Clarified pregnancy reporting - Updated ADA blood draw schedule for single-agent maintenance therapy as Week 1 of every third cycle - Updated single-agent blood draw schedule and amount of blood to be collected - 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" - Included both references to Federal Code of Regulations and ICH Guidelines in regards to the inclusion of the elements of an informed consent form - Clarified subject confidentiality - Clarification of data management plan, eCRF details and study materials - Clarified the instructions and regulations for required retention of data
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: