



Clinical trial results:

A Randomized, Double-blind, Multi-center Phase 2 Trial of Denosumab in Combination With Chemotherapy as First-line Treatment of Metastatic Non-small Cell Lung Cancer

Summary

EudraCT number	2013-001662-42
Trial protocol	DE NL IT GB GR CZ
Global end of trial date	28 November 2017

Results information

Result version number	v1 (current)
This version publication date	07 December 2018
First version publication date	07 December 2018

Trial information

Trial identification

Sponsor protocol code	20120249
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01951586
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

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	28 November 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the treatment effect of the combination of denosumab and standard of care (SOC) versus SOC alone on overall survival.

Protection of trial subjects:

This study was conducted in accordance with the current version of the Declaration of Helsinki, and the Food and Drug Administration and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Greece: 31
Worldwide total number of subjects	226
EEA total number of subjects	133

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	113
From 65 to 84 years	112
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 57 centers in 10 countries including the United Kingdom, Netherlands, France, Italy, Germany, Czech Republic, United States, Canada, Australia and Greece. Participants were enrolled from 31 December 2013 to 21 May 2015.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to receive denosumab or placebo. Randomization was stratified based on the presence of bone metastasis (yes or no), histology (squamous versus non-squamous), and geographic region (North America, Western Europe/Australia, and rest of world [ROW]).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomized to receive placebo matching to denosumab by subcutaneous injection once every 4 weeks (Q4W) plus one loading dose on study day 8 in addition to platinum-based standard chemotherapy. Participants may have received placebo as often as once every 3 weeks (Q3W) while receiving Q3W chemotherapy. Participants with bone metastases also received 4 mg zoledronic acid administered as an IV infusion Q4W or Q3W.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once every 4 weeks (Q4W) plus one loading dose on study day 8; could be administered as often as every 3 weeks (Q3W) to participants receiving Q3W chemotherapy.

Arm title	Denosumab
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Arm description:

Participants randomized to receive 120 mg denosumab by subcutaneous injection once every 4 weeks plus one loading dose on study day 8 in addition to platinum-based standard chemotherapy. Participants may have received denosumab as often as Q3W while receiving Q3W chemotherapy. Participants with bone metastases also received placebo to zoledronic acid administered as an IV infusion Q4W or Q3W.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	AMG 162
Other name	XGEVA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once every 4 weeks (Q4W) plus one loading dose on study day 8; could be administered as often as every 3 weeks (Q3W) to participants receiving Q3W chemotherapy.

Number of subjects in period 1	Placebo	Denosumab
Started	78	148
Received Study Drug	76	145
Completed	0	0
Not completed	78	148
Consent withdrawn by subject	8	17
Death	61	120
Lost to follow-up	-	1
Decision by sponsor	9	10

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive placebo matching to denosumab by subcutaneous injection once every 4 weeks (Q4W) plus one loading dose on study day 8 in addition to platinum-based standard chemotherapy. Participants may have received placebo as often as once every 3 weeks (Q3W) while receiving Q3W chemotherapy. Participants with bone metastases also received 4 mg zoledronic acid administered as an IV infusion Q4W or Q3W.	
Reporting group title	Denosumab
Reporting group description:	
Participants randomized to receive 120 mg denosumab by subcutaneous injection once every 4 weeks plus one loading dose on study day 8 in addition to platinum-based standard chemotherapy. Participants may have received denosumab as often as Q3W while receiving Q3W chemotherapy. Participants with bone metastases also received placebo to zoledronic acid administered as an IV infusion Q4W or Q3W.	

Reporting group values	Placebo	Denosumab	Total
Number of subjects	78	148	226
Age categorical			
Units: Subjects			
< 70 years	54	102	156
≥ 70 years	24	46	70
Age Continuous			
Units: years			
arithmetic mean	64.0	63.8	-
standard deviation	± 10.1	± 9.7	
Sex: Female, Male			
Units: Subjects			
Female	20	54	74
Male	58	94	152
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	2	7	9
White or Caucasian	73	133	206
Others	3	8	11
Presence of Bone Metastasis			
Data are based on randomized strata.			
Units: Subjects			
Yes	35	65	100
No	43	83	126
Histology			
Data are based on randomized strata.			
Units: Subjects			
Squamous	18	35	53
Non-squamous	60	113	173
Geographic region			
Units: Subjects			
North America/Australia	30	63	93
Western Europe	35	67	102
Rest of World	13	18	31

Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a participants disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. 0 = Fully Active; 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self- Care; 4 = Completely Disabled, no self-care, confined to bed or chair; 5 = Dead.			
Units: Subjects			
0 (Fully active)	33	69	102
1 (Restrictive but ambulatory)	45	79	124
Time from Initial Diagnosis of NSCLC to Randomization			
Units: months			
arithmetic mean	2.46	6.32	
standard deviation	± 5.28	± 16.96	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants randomized to receive placebo matching to denosumab by subcutaneous injection once every 4 weeks (Q4W) plus one loading dose on study day 8 in addition to platinum-based standard chemotherapy. Participants may have received placebo as often as once every 3 weeks (Q3W) while receiving Q3W chemotherapy. Participants with bone metastases also received 4 mg zoledronic acid administered as an IV infusion Q4W or Q3W.	
Reporting group title	Denosumab
Reporting group description: Participants randomized to receive 120 mg denosumab by subcutaneous injection once every 4 weeks plus one loading dose on study day 8 in addition to platinum-based standard chemotherapy. Participants may have received denosumab as often as Q3W while receiving Q3W chemotherapy. Participants with bone metastases also received placebo to zoledronic acid administered as an IV infusion Q4W or Q3W.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: Overall survival was calculated as the time from the date of randomization to the date of death from any cause. Participants last known to be alive were censored at the last contact date. The analysis includes all randomized participants.	
End point type	Primary
End point timeframe: From randomization until the end of study; median time on study was 9.64 months.	

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	148		
Units: months				
median (confidence interval 95%)	10.9 (9.26 to 15.54)	10.7 (8.54 to 12.35)		

Statistical analyses

Statistical analysis title	Final Analysis of Overall Survival
Statistical analysis description: Overall survival was analyzed using a Cox proportional hazard model with treatment groups as the independent variable and stratified by the randomization stratification factors. A hazard ratio < 1 favors denosumab.	
Comparison groups	Placebo v Denosumab

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5157 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.53

Notes:

[1] - Log rank test stratified by the randomization stratification factors (presence of bone metastasis [yes or no], histology [squamous versus non-squamous], geographic region [North America, Western Europe/Australia, rest of world]).

Secondary: Correlation of Tumor Tissue RANK Expression with Overall Survival

End point title	Correlation of Tumor Tissue RANK Expression with Overall Survival
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End point description:

To assess whether the treatment effect on overall survival was correlated with receptor activator of nuclear factor (NF)-κB (RANK) protein expression in tumor cells, RANK expression in archival tumor samples was measured using immunohistochemistry. The intensity of stain in the cytoplasm, membrane, and total was categorized as 0 (negative), 1+ (weak), 2+ (moderate) or 3+ (strong); All intensity is the sum of levels +1, +2 and +3. In addition, an H-score was calculated using the following formula: H-score=(percentage of cells of weak×1)+(percentage of cells of moderate×2)+(percentage of cells of strong×3). The maximum H-score was 300, corresponding to 100% of cells with strong intensity. The correlation between RANK expression level and OS was evaluated using a Cox proportional hazard models that included RANK expression level stratified by the randomization stratification factors in the corresponding treatment group.

End point type	Secondary
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End point timeframe:

From randomization until the data cut-off date of 29 July 2016; median time on study was 9.64 months.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64 ^[2]	123 ^[3]		
Units: hazard ratio				
number (confidence interval 95%)				
Cytoplasm all intensity	0.84 (0.65 to 1.09)	1.00 (0.85 to 1.17)		
Membrane all intensity	0.72 (0.51 to 1.01)	0.92 (0.74 to 1.14)		
Total all intensity	0.80 (0.62 to 1.03)	1.00 (0.85 to 1.17)		
Cytoplasm H-score	0.83 (0.65 to 1.07)	1.00 (0.86 to 1.16)		
Membrane H-score	0.72 (0.52 to 1.00)	0.93 (0.77 to 1.13)		
Total H-score	0.80 (0.62 to 1.02)	1.00 (0.86 to 1.16)		

Notes:

[2] - All randomized participants who had evaluable pre-treatment tumor RANK expression

[3] - All randomized participants who had evaluable pre-treatment tumor RANK expression

Statistical analyses

Statistical analysis title	Treatment-by-biomarker Interaction
Statistical analysis description: The interaction of RANK expression level measured in the cytoplasm (all intensity) and treatment effect was evaluated using a Cox proportional hazard model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3759
Method	Cox propotional hazard model

Statistical analysis title	Treatment-by-biomarker Interaction
Statistical analysis description: The interaction of RANK expression level measured in membranes (all intensity) and treatment effect was evaluated using a Cox proportional hazard model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3666
Method	Cox propotional hazard model

Statistical analysis title	Treatment-by-biomarker Interaction
Statistical analysis description: The interaction of RANK expression level total (cytoplasm + membranes; all intensity) and treatment effect was evaluated using a Cox proportional hazard model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1917
Method	Cox propotional hazard model

Statistical analysis title	Treatment-by-biomarker Interaction
Statistical analysis description: The interaction of RANK expression level measured in the cytoplasm (H-score) and treatment effect was evaluated using a Cox proportional hazard model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3353
Method	Cox propotional hazard model

Statistical analysis title	Treatment-by-biomarker Interaction
Statistical analysis description: The interaction of RANK expression level measured in membranes (H-score) and treatment effect was evaluated using a Cox proportional hazard model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3179
Method	Cox propotional hazard model

Statistical analysis title	Treatment-by-biomarker Interaction
Statistical analysis description: The interaction of RANK expression level total (cytoplasm + membranes; H-score) and treatment effect was evaluated using a Cox proportional hazard model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1583
Method	Cox propotional hazard model

Secondary: Correlation of Tumor Tissue RANK Ligand Expression with Overall Survival

End point title	Correlation of Tumor Tissue RANK Ligand Expression with Overall Survival
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End point description:

To assess whether the treatment effect on overall survival was correlated with RANK ligand (RANKL)

protein expression in tumor cells, RANKL expression in archival tumor samples was measured using immunohistochemistry. The intensity of stain in the cytoplasm was categorized as 0 (negative), 1+ (weak), 2+ (moderate) or 3+ (strong); All intensity is the sum of levels +1, +2 and +3. In addition, an H-score was calculated using the following formula: H-score=(percentage of cells of weak×1)+(percentage of cells of moderate×2)+(percentage of cells of strong×3). The maximum H-score was 300, corresponding to 100% of cells with strong intensity. The correlation between RANKL expression level and OS was evaluated using a Cox proportional hazard models that included RANKL expression level stratified by the randomization stratification factors in the corresponding treatment

End point type	Secondary
End point timeframe:	
From randomization until the data cut-off date of 29 July 2016; median time on study was 9.64 months.	

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65 ^[4]	121 ^[5]		
Units: hazard ratio				
number (confidence interval 95%)				
Cytoplasm all intensity	0.77 (0.63 to 0.95)	0.93 (0.82 to 1.05)		
Cytoplasm H-score	0.79 (0.66 to 0.95)	0.93 (0.84 to 1.04)		

Notes:

[4] - All randomized participants who had evaluable pre-treatment tumor RANKL expression

[5] - All randomized participants who had evaluable pre-treatment tumor RANKL expression

Statistical analyses

Statistical analysis title	Treatment-by-biomarker Interaction
Statistical analysis description:	
The interaction of RANKL expression level measured in the cytoplasm (H-score) and treatment effect was evaluated using a Cox proportional hazard model that included treatment group, RANKL expression level and treatment-by-RANKL expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3735
Method	Cox propotional hazard model

Statistical analysis title	Treatment-by-biomarker Interaction
Statistical analysis description:	
The interaction of RANKL expression level measured in the cytoplasm (all intensity) and treatment effect was evaluated using a Cox proportional hazard model that included treatment group, RANKL expression level and treatment-by-RANKL expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3946
Method	Cox propotional hazard model

Secondary: Objective Response Rate

End point title	Objective Response Rate
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End point description:

Objective response rate was defined as the percentage of participants with a complete response (CR) or partial response (PR) based on modified RECIST 1.1 achieved over the study duration. CR:

Disappearance of all target and non target lesions, normalization of tumor marker levels and no new lesions. PR: At least a 30% decrease in the size of target lesions with no progression of non-target lesions and no new lesions, or, disappearance of target lesions with persistence of one or more non-target lesions and/or maintenance of tumor marker levels above normal limits and no new lesions.

Participants who underwent surgical resection while on study were not evaluated for response after the surgery. Participants who did not meet the criteria for an objective response by the analysis cutoff date were considered non-responders.

Response rate was analyzed in randomized participants with at least one baseline measurable lesion per modified RECIST 1.1.

End point type	Secondary
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End point timeframe:

From randomization until the data cut-off date of 29 July 2016; median time on study was 9.64 months.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	144		
Units: percentage of participants				
number (not applicable)	43.4	36.8		

Statistical analyses

Statistical analysis title	Analysis of Objective Response Rate
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Statistical analysis description:

Odds ration was based on a logistic regression model adjusted for the randomization stratification factors; an odds ratio ≥ 1 favors denosumab.

Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3491 ^[6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.35

Notes:

[6] - Logistic regression model adjusted for the randomization stratification factors (presence of bone metastasis [yes or no], histology [squamous versus non-squamous], geographic region [North America, Western Europe/Australia, rest of world]).

Secondary: Correlation of Tumor Tissue RANK Expression with Objective Response Rate

End point title	Correlation of Tumor Tissue RANK Expression with Objective Response Rate
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End point description:

To assess whether the treatment effect on objective response rate (ORR) based on RECIST 1.1 was correlated with RANK protein expression in tumor cells, RANK expression in archival tumor samples was measured using immunohistochemistry. The intensity of stain in the cytoplasm, membrane, and total was categorized as 0 (negative), 1+ (weak), 2+ (moderate) or 3+ (strong); All intensity is the sum of levels +1, +2 and +3. In addition, an H-score was calculated using the following formula: H-score=(percentage of cells of weak×1)+(percentage of cells of moderate×2)+(percentage of cells of strong×3). The maximum H-score was 300, corresponding to 100% of cells with strong intensity. The correlation between RANK expression level and ORR was evaluated within each treatment group using a logistical regression model that included RANK expression value as an independent variable and stratified by the randomization stratification factors. The odds ratio and 95% confidence interval are reported.

End point type	Secondary
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End point timeframe:

From randomization until the data cut-off date of 29 July 2016; median time on study was 9.64 months.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63 ^[7]	119 ^[8]		
Units: odds ratio				
number (confidence interval 95%)				
Cytoplasm all intensity	1.00 (0.67 to 1.50)	0.88 (0.68 to 1.13)		
Membrane all intensity	1.18 (0.74 to 1.89)	0.82 (0.57 to 1.17)		
Total all intensity	1.16 (0.78 to 1.71)	0.88 (0.68 to 1.13)		
Cytoplasm H-score	1.00 (0.69 to 1.47)	0.87 (0.68 to 1.11)		
Membrane H-score	1.14 (0.74 to 1.76)	0.82 (0.59 to 1.14)		
Total H-score	1.14 (0.79 to 1.65)	0.87 (0.69 to 1.11)		

Notes:

[7] - Participants with ≥ 1 baseline measurable lesion and evaluable pre-treatment tumor RANK expression

[8] - Participants with ≥ 1 baseline measurable lesion and evaluable pre-treatment tumor RANK expression

Statistical analyses

Statistical analysis title	Treatment-by-RANK Interaction
Statistical analysis description:	
The interaction of RANK expression level measured in the cytoplasm (all intensity) and treatment effect was evaluated using a logistic regression model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.476
Method	Regression, Logistic

Statistical analysis title	Treatment-by-RANK Interaction
Statistical analysis description:	
The interaction of RANK expression level measured in the membranes (all intensity) and treatment effect was evaluated using a logistic regression model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2582
Method	Regression, Logistic

Statistical analysis title	Treatment-by-RANK Interaction
Statistical analysis description:	
The interaction of RANK expression level total (cytoplasm + membrane; all intensity) and treatment effect was evaluated using a logistic regression model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.223
Method	Regression, Logistic

Statistical analysis title	Treatment-by-RANK Interaction
Statistical analysis description:	
The interaction of RANK expression level measured in the cytoplasm (H-score) and treatment effect was evaluated using a logistic regression model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4329
Method	Regression, Logistic

Statistical analysis title	Treatment-by-RANK Interaction
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Statistical analysis description:

The interaction of RANK expression level measured in the membranes (H-score) and treatment effect was evaluated using a logistic regression model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.

Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.262
Method	Regression, Logistic

Statistical analysis title	Treatment-by-RANK Interaction
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Statistical analysis description:

The interaction of RANK expression level total (cytoplasm + membrane; H-score) and treatment effect was evaluated using a logistic regression model that included treatment group, RANK expression level and treatment-by-RANK expression level interaction stratified by the randomization stratification factors.

Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2081
Method	Regression, Logistic

Secondary: Correlation of Tumor Tissue RANKL Expression with Objective Response Rate

End point title	Correlation of Tumor Tissue RANKL Expression with Objective Response Rate
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End point description:

To assess whether the treatment effect on objective response rate (ORR) based on RECIST 1.1 was correlated with RANKL protein expression in tumor cells, RANKL expression in archival tumor samples was measured using immunohistochemistry. The intensity of stain in the cytoplasm was categorized as 0 (negative), 1+ (weak), 2+ (moderate) or 3+ (strong); All intensity is the sum of levels +1, +2 and +3. In addition, an H-score was calculated using the following formula: H-score=(percentage of cells of weak×1)+(percentage of cells of moderate×2)+(percentage of cells of strong×3). The maximum H-score was 300, corresponding to 100% of cells with strong intensity. The correlation between RANKL expression level and ORR was evaluated within each treatment group using a logistical regression model that included RANKL expression value as an independent variable and stratified by the randomization stratification factors. The odds ratio and 95% confidence interval are reported.

End point type	Secondary
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End point timeframe:

From randomization until the data cut-off date of 29 July 2016; median time on study was 9.64 months.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64 ^[9]	117 ^[10]		
Units: odds ratio				
number (confidence interval 95%)				
Cytoplasm all intensity	1.27 (0.88 to 1.83)	1.10 (0.90 to 1.35)		
Cytoplasm H-score	1.25 (0.91 to 1.72)	1.09 (0.91 to 1.30)		

Notes:

[9] - Participants with ≥ 1 baseline measurable lesion and evaluable pre-treatment tumor RANKL expression

[10] - Participants with ≥ 1 baseline measurable lesion and evaluable pre-treatment tumor RANKL expression

Statistical analyses

Statistical analysis title	Treatment-by-RANKL Interaction
Statistical analysis description:	
The interaction of RANKL expression level measured in the cytoplasm (H-score) and treatment effect was evaluated using a logistic regression model that included treatment group, RANKL expression level and treatment-by-RANKL expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4236
Method	Regression, Logistic

Statistical analysis title	Treatment-by-RANKL Interaction
Statistical analysis description:	
The interaction of RANKL expression level measured in the cytoplasm (all intensity) and treatment effect was evaluated using a logistic regression model that included treatment group, RANKL expression level and treatment-by-RANKL expression level interaction stratified by the randomization stratification factors.	
Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4671
Method	Regression, Logistic

Secondary: Clinical Benefit Rate

End point title	Clinical Benefit Rate
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End point description:

Clinical benefit rate was defined as the percentage of participants with an objective response (CR or PR) or stable disease (SD) or better for at least 16 weeks achieved over the study duration. If a participant underwent surgical resection while on study, the participant was not evaluated for response after the surgery. Participants who did not meet the criteria for clinical benefit by the analysis cutoff date were considered as non-responders.

Clinical benefit rate was analyzed in randomized participants with at least one baseline measurable lesion per modified RECIST 1.1.

End point type	Secondary
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End point timeframe:

From randomization until the data cut-off date of 29 July 2016; median time on study was 9.64 months.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	144		
Units: percentage of participants				
number (not applicable)	53.9	47.9		

Statistical analyses

Statistical analysis title	Analysis of Clinical Benefit Rate
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Statistical analysis description:

The odds ratio is based on a logistic regression model adjusted for the randomization stratification factors; an odds ratio ≥ 1 favors denosumab.

Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4654 ^[11]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.43

Notes:

[11] - Logistic regression model adjusted for the randomization stratification factors (presence of bone metastasis [yes or no], histology [squamous versus non-squamous], geographic region [North America, Western Europe/Australia, rest of world]).

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
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End point description:

Progression-free survival was defined as the time from randomization to the first observed disease progression per modified RECIST 1.1 criteria or death from any cause. Participants last known to be alive who did not experience disease progression were censored at their last imaging assessment date, last contact date if they were in the survival follow up phase, end of the study date, or the primary analysis cut-off date, whichever was first. If a participant underwent surgical resection while on study,

the participant was censored at the last evaluable imaging assessment prior to the surgery.
The analysis includes all randomized participants.

End point type	Secondary
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End point timeframe:

From randomization until the data cut-off date of 29 July 2016; median time on study was 9.64 months.

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	148		
Units: months				
median (confidence interval 95%)	5.7 (4.37 to 7.16)	5.2 (4.24 to 5.78)		

Statistical analyses

Statistical analysis title	Analysis of Progression-free Survival
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Statistical analysis description:

The hazard ratio is based on a Cox proportional hazards model stratified by the randomization stratification factors. A hazard ratio < 1 favors denosumab.

Comparison groups	Placebo v Denosumab
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7363 ^[12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.43

Notes:

[12] - Log rank test stratified by the randomization stratification factors (presence of bone metastasis [yes or no], histology [squamous versus non-squamous], geographic region [North America, Western Europe/Australia, rest of world]).

Secondary: Serum Denosumab Trough Levels in Participants who Received Q3W Dosing

End point title	Serum Denosumab Trough Levels in Participants who Received Q3W Dosing ^[13]
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End point description:

Serum samples were analyzed for denosumab using enzyme-linked immunosorbent assay (ELISA) following a validated procedure. The lower limit of quantification for the assay was 20 ng/mL. The analysis includes randomized participants who received denosumab every 3 weeks with at least one valid denosumab concentration measurement.

End point type	Secondary
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End point timeframe:

Prior to dosing at day 8 and weeks 3, 6, 9, 12, 15, 18, 21 and 24.

Notes:

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

Justification: Trough serum denosumab was analyzed separately for participants who received Q4W and Q3W dosing.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	104			
Units: ng/mL				
arithmetic mean (standard deviation)				
Dose 2 - Day 8 (n = 63)	8590 (± 4080)			
Dose 3 - Week 3 (n = 17)	12200 (± 5710)			
Dose 4 - Week 6 (n = 46)	19700 (± 7350)			
Dose 5 - Week 9 (n = 56)	19600 (± 8270)			
Dose 6 - Week 12 (n = 51)	22800 (± 10400)			
Dose 7 - Week 15 (n = 46)	24300 (± 11500)			
Dose 8 - Week 18 (n = 40)	22700 (± 10600)			
Dose 9 - Week 21 (n = 31)	22100 (± 11200)			
Dose 10 - Week 24 (n = 28)	23300 (± 12700)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Denosumab Trough Levels in Participants who Received Q4W Dosing

End point title	Serum Denosumab Trough Levels in Participants who Received Q4W Dosing ^[14]
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End point description:

Serum samples were analyzed for denosumab using enzyme-linked immunosorbent assay (ELISA) following a validated procedure. The lower limit of quantification for the assay was 20 ng/mL.

The analysis includes randomized participants who received denosumab every 4 weeks with at least one valid denosumab concentration measurement.

End point type	Secondary
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End point timeframe:

Prior to dosing at day 8 and weeks 4, 8, 12, 16, 20 and 24

Notes:

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

Justification: Trough serum denosumab was analyzed separately for participants who received Q4W and Q3W dosing.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
arithmetic mean (standard deviation)				
Dose 2 - Day 8 (n = 4)	8990 (± 2470)			
Dose 3 - Week 4 (n = 4)	10900 (± 3170)			
Dose 4 - Week 8 (n = 3)	15700 (± 6710)			
Dose 5 - Week 12 (n = 6)	14500 (± 4940)			
Dose 6 - Week 16 (n = 5)	13000 (± 4380)			
Dose 7 - Week 20 (n = 6)	15400 (± 5620)			
Dose 8 - Week 24 (n = 4)	15900 (± 7810)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-emergent Adverse Events

End point title	Number of Participants with Treatment-emergent Adverse Events
End point description: The analysis includes all randomized participants who received at least one dose of study drug. Participants were analyzed according to the actual treatment received; participants who received at least one dose of denosumab were analyzed in the "Denosumab" treatment group regardless of the randomized treatment assigned.	
End point type	Secondary
End point timeframe: From first dose of study drug to the end of study date; the median (min, max) duration was 10.0 (0.2, 41.4) and 9.4 (0.2, 42.9) months for Placebo and Denosumab respectively.	

End point values	Placebo	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	145		
Units: participants				
All adverse events (AEs)	76	144		
Serious adverse events	68	129		
AEs leading to discontinuation of study drug	6	20		
Fatal adverse events	53	113		
Treatment-related adverse events (TRAEs)	24	51		
Treatment-related serious adverse events	0	6		

TRAEs leading to discontinuation of study drug	0	7		
Treatment-related fatal adverse events	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to the end of study date; the median (min, max) duration was 10.0 (0.2, 41.4) and 9.4 (0.2, 42.9) months for Placebo and Denosumab respectively.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Denosumab
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Reporting group description:

Participants received 120 mg denosumab by subcutaneous injection once every 4 weeks plus one loading dose on study day 8 in addition to platinum-based standard chemotherapy. Participants may have received denosumab as often as Q3W while receiving Q3W chemotherapy. Participants with bone metastases also received placebo to zoledronic acid administered as an IV infusion Q4W or Q3W.

Reporting group title	Placebo
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Reporting group description:

Participants received placebo matching to denosumab by subcutaneous injection once every 4 weeks (Q4W) plus one loading dose on study day 8 in addition to platinum-based standard chemotherapy. Participants may have received placebo as often as once every 3 weeks (Q3W) while receiving Q3W chemotherapy. Participants with bone metastases also received 4 mg zoledronic acid administered as an IV infusion Q4W or Q3W.

Serious adverse events	Denosumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	129 / 145 (88.97%)	68 / 76 (89.47%)	
number of deaths (all causes)	118	59	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	4 / 145 (2.76%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Bronchial carcinoma			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	2 / 145 (1.38%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Lung adenocarcinoma stage IV			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	9 / 145 (6.21%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 9	0 / 3	
Lung neoplasm malignant			
subjects affected / exposed	10 / 145 (6.90%)	5 / 76 (6.58%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 10	0 / 4	
Lung squamous cell carcinoma metastatic			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	2 / 145 (1.38%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Malignant pleural effusion			

subjects affected / exposed	1 / 145 (0.69%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 145 (0.00%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone marrow			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	6 / 145 (4.14%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 10	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 1	
Metastases to lung			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to meninges			
subjects affected / exposed	2 / 145 (1.38%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 145 (0.00%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Non-small cell lung cancer			
subjects affected / exposed	19 / 145 (13.10%)	9 / 76 (11.84%)	
occurrences causally related to treatment / all	0 / 19	0 / 10	
deaths causally related to treatment / all	0 / 18	0 / 9	
Non-small cell lung cancer metastatic			

subjects affected / exposed	14 / 145 (9.66%)	7 / 76 (9.21%)	
occurrences causally related to treatment / all	0 / 14	0 / 7	
deaths causally related to treatment / all	0 / 14	0 / 7	
Non-small cell lung cancer stage IV			
subjects affected / exposed	12 / 145 (8.28%)	5 / 76 (6.58%)	
occurrences causally related to treatment / all	0 / 14	0 / 7	
deaths causally related to treatment / all	0 / 11	0 / 5	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 145 (0.69%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension			
subjects affected / exposed	4 / 145 (2.76%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Jugular vein thrombosis			

subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	4 / 145 (2.76%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	5 / 145 (3.45%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 1	
Condition aggravated			
subjects affected / exposed	1 / 145 (0.69%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	2 / 145 (1.38%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	7 / 145 (4.83%)	4 / 76 (5.26%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 2	
Infusion site extravasation			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 145 (0.00%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	12 / 145 (8.28%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 18	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory distress syndrome			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 145 (3.45%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	16 / 145 (11.03%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 20	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 145 (0.69%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 145 (1.38%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemothorax			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 145 (1.38%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal mass			

subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Laryngeal obstruction			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	6 / 145 (4.14%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 145 (2.07%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 145 (4.14%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			

subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	3 / 145 (2.07%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	4 / 145 (2.76%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 145 (2.07%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			

Device issue			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nutritional condition abnormal			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 145 (0.69%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radiation oesophagitis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 145 (0.69%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 145 (2.07%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardio-respiratory arrest			
subjects affected / exposed	4 / 145 (2.76%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 3	
Myocardial infarction			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachycardia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	2 / 145 (1.38%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 145 (1.38%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Consciousness fluctuating			

subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	2 / 145 (1.38%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 145 (3.45%)	5 / 76 (6.58%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 145 (4.14%)	5 / 76 (6.58%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 145 (2.07%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 145 (1.38%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	4 / 145 (2.76%)	5 / 76 (6.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 145 (0.69%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	6 / 145 (4.14%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	2 / 145 (1.38%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	4 / 145 (2.76%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 145 (0.69%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haemorrhage			

subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	2 / 145 (1.38%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 145 (1.38%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 145 (0.69%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	4 / 145 (2.76%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral lesion			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 145 (0.69%) 0 / 2 0 / 0	0 / 76 (0.00%) 0 / 0 0 / 0	
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 145 (1.38%) 0 / 2 0 / 0	1 / 76 (1.32%) 0 / 1 0 / 0	
Fungal infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 145 (0.00%) 0 / 0 0 / 0	1 / 76 (1.32%) 0 / 1 0 / 0	
Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 145 (0.69%) 0 / 1 0 / 0	1 / 76 (1.32%) 0 / 1 0 / 0	
Gangrene subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 145 (0.69%) 0 / 1 0 / 0	0 / 76 (0.00%) 0 / 0 0 / 0	
Gastroenteritis shigella subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 145 (0.69%) 0 / 1 0 / 0	0 / 76 (0.00%) 0 / 0 0 / 0	
Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 145 (0.69%) 0 / 1 0 / 0	2 / 76 (2.63%) 0 / 2 0 / 0	
Lung abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 145 (0.69%) 0 / 1 0 / 0	0 / 76 (0.00%) 0 / 0 0 / 0	
Lung infection			

subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	1 / 145 (0.69%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	14 / 145 (9.66%)	7 / 76 (9.21%)	
occurrences causally related to treatment / all	0 / 19	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 145 (2.07%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 145 (1.38%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 145 (2.07%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	1 / 145 (0.69%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dehydration			
subjects affected / exposed	6 / 145 (4.14%)	2 / 76 (2.63%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 145 (1.38%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Denosumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 145 (95.86%)	71 / 76 (93.42%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 145 (2.76%)	5 / 76 (6.58%)	
occurrences (all)	4	6	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	24 / 145 (16.55%)	8 / 76 (10.53%)	
occurrences (all)	30	18	
Fatigue			
subjects affected / exposed	67 / 145 (46.21%)	33 / 76 (43.42%)	
occurrences (all)	112	55	
Mucosal inflammation			
subjects affected / exposed	8 / 145 (5.52%)	4 / 76 (5.26%)	
occurrences (all)	13	5	
Oedema peripheral			
subjects affected / exposed	26 / 145 (17.93%)	17 / 76 (22.37%)	
occurrences (all)	33	19	
Pyrexia			
subjects affected / exposed	23 / 145 (15.86%)	9 / 76 (11.84%)	
occurrences (all)	33	12	
Pain			
subjects affected / exposed	10 / 145 (6.90%)	7 / 76 (9.21%)	
occurrences (all)	11	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 145 (17.93%)	16 / 76 (21.05%)	
occurrences (all)	35	17	
Dyspnoea			
subjects affected / exposed	35 / 145 (24.14%)	18 / 76 (23.68%)	
occurrences (all)	46	21	
Epistaxis			
subjects affected / exposed	8 / 145 (5.52%)	5 / 76 (6.58%)	
occurrences (all)	9	5	
Haemoptysis			
subjects affected / exposed	10 / 145 (6.90%)	6 / 76 (7.89%)	
occurrences (all)	11	8	
Hiccups			
subjects affected / exposed	7 / 145 (4.83%)	4 / 76 (5.26%)	
occurrences (all)	7	4	
Productive cough			

subjects affected / exposed occurrences (all)	9 / 145 (6.21%) 11	2 / 76 (2.63%) 2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	14 / 145 (9.66%)	5 / 76 (6.58%)	
occurrences (all)	17	5	
Depression			
subjects affected / exposed	2 / 145 (1.38%)	6 / 76 (7.89%)	
occurrences (all)	2	6	
Insomnia			
subjects affected / exposed	12 / 145 (8.28%)	7 / 76 (9.21%)	
occurrences (all)	13	7	
Investigations			
Blood creatinine increased			
subjects affected / exposed	12 / 145 (8.28%)	3 / 76 (3.95%)	
occurrences (all)	26	5	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 145 (2.07%)	4 / 76 (5.26%)	
occurrences (all)	3	6	
Platelet count decreased			
subjects affected / exposed	14 / 145 (9.66%)	8 / 76 (10.53%)	
occurrences (all)	25	11	
Weight decreased			
subjects affected / exposed	8 / 145 (5.52%)	10 / 76 (13.16%)	
occurrences (all)	9	13	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 145 (1.38%)	5 / 76 (6.58%)	
occurrences (all)	2	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	20 / 145 (13.79%)	7 / 76 (9.21%)	
occurrences (all)	21	9	
Dysgeusia			
subjects affected / exposed	8 / 145 (5.52%)	11 / 76 (14.47%)	
occurrences (all)	8	12	

Headache subjects affected / exposed occurrences (all)	24 / 145 (16.55%) 30	8 / 76 (10.53%) 8	
Neuropathy peripheral subjects affected / exposed occurrences (all)	5 / 145 (3.45%) 5	9 / 76 (11.84%) 11	
Paraesthesia subjects affected / exposed occurrences (all)	8 / 145 (5.52%) 12	2 / 76 (2.63%) 2	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	60 / 145 (41.38%) 156	38 / 76 (50.00%) 101	
Neutropenia subjects affected / exposed occurrences (all)	32 / 145 (22.07%) 77	15 / 76 (19.74%) 32	
Thrombocytopenia subjects affected / exposed occurrences (all)	16 / 145 (11.03%) 37	16 / 76 (21.05%) 27	
Leukopenia subjects affected / exposed occurrences (all)	6 / 145 (4.14%) 14	4 / 76 (5.26%) 7	
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	2 / 145 (1.38%) 2	4 / 76 (5.26%) 5	
Lacrimation increased subjects affected / exposed occurrences (all)	9 / 145 (6.21%) 10	3 / 76 (3.95%) 5	
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	1 / 145 (0.69%) 1	4 / 76 (5.26%) 4	
Abdominal pain subjects affected / exposed occurrences (all)	13 / 145 (8.97%) 13	4 / 76 (5.26%) 5	
Constipation			

subjects affected / exposed	50 / 145 (34.48%)	27 / 76 (35.53%)	
occurrences (all)	70	35	
Diarrhoea			
subjects affected / exposed	26 / 145 (17.93%)	14 / 76 (18.42%)	
occurrences (all)	29	16	
Dyspepsia			
subjects affected / exposed	8 / 145 (5.52%)	5 / 76 (6.58%)	
occurrences (all)	10	5	
Dysphagia			
subjects affected / exposed	5 / 145 (3.45%)	6 / 76 (7.89%)	
occurrences (all)	7	7	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 145 (4.14%)	4 / 76 (5.26%)	
occurrences (all)	6	4	
Nausea			
subjects affected / exposed	64 / 145 (44.14%)	34 / 76 (44.74%)	
occurrences (all)	105	53	
Vomiting			
subjects affected / exposed	35 / 145 (24.14%)	14 / 76 (18.42%)	
occurrences (all)	57	19	
Stomatitis			
subjects affected / exposed	7 / 145 (4.83%)	6 / 76 (7.89%)	
occurrences (all)	11	9	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	9 / 145 (6.21%)	6 / 76 (7.89%)	
occurrences (all)	9	6	
Dry skin			
subjects affected / exposed	6 / 145 (4.14%)	4 / 76 (5.26%)	
occurrences (all)	6	4	
Rash			
subjects affected / exposed	18 / 145 (12.41%)	8 / 76 (10.53%)	
occurrences (all)	21	11	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	11 / 145 (7.59%)	7 / 76 (9.21%)	
occurrences (all)	15	8	
Back pain			
subjects affected / exposed	20 / 145 (13.79%)	15 / 76 (19.74%)	
occurrences (all)	23	24	
Muscle spasms			
subjects affected / exposed	4 / 145 (2.76%)	4 / 76 (5.26%)	
occurrences (all)	4	4	
Musculoskeletal chest pain			
subjects affected / exposed	9 / 145 (6.21%)	5 / 76 (6.58%)	
occurrences (all)	9	10	
Pain in extremity			
subjects affected / exposed	14 / 145 (9.66%)	7 / 76 (9.21%)	
occurrences (all)	22	10	
Musculoskeletal pain			
subjects affected / exposed	10 / 145 (6.90%)	5 / 76 (6.58%)	
occurrences (all)	14	6	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 145 (0.00%)	4 / 76 (5.26%)	
occurrences (all)	0	5	
Oral candidiasis			
subjects affected / exposed	5 / 145 (3.45%)	5 / 76 (6.58%)	
occurrences (all)	6	6	
Nasopharyngitis			
subjects affected / exposed	3 / 145 (2.07%)	5 / 76 (6.58%)	
occurrences (all)	3	6	
Urinary tract infection			
subjects affected / exposed	11 / 145 (7.59%)	4 / 76 (5.26%)	
occurrences (all)	12	4	
Pneumonia			
subjects affected / exposed	10 / 145 (6.90%)	2 / 76 (2.63%)	
occurrences (all)	11	2	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	34 / 145 (23.45%) 39	23 / 76 (30.26%) 30	
Hypercalcaemia subjects affected / exposed occurrences (all)	5 / 145 (3.45%) 5	4 / 76 (5.26%) 4	
Hyperglycaemia subjects affected / exposed occurrences (all)	6 / 145 (4.14%) 8	4 / 76 (5.26%) 4	
Hypokalaemia subjects affected / exposed occurrences (all)	8 / 145 (5.52%) 9	4 / 76 (5.26%) 4	
Hypocalcaemia subjects affected / exposed occurrences (all)	24 / 145 (16.55%) 39	4 / 76 (5.26%) 6	
Hypomagnesaemia subjects affected / exposed occurrences (all)	17 / 145 (11.72%) 28	12 / 76 (15.79%) 19	
Hyponatraemia subjects affected / exposed occurrences (all)	3 / 145 (2.07%) 4	4 / 76 (5.26%) 4	
Hypophosphataemia subjects affected / exposed occurrences (all)	11 / 145 (7.59%) 15	5 / 76 (6.58%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2014	<ul style="list-style-type: none">• to clarify that randomization must be before the first dose (cycle 1 day 1) of the planned chemotherapy described in the protocol• modify the duration after the last dose of investigational product for using contraception, becoming pregnant, and breast feeding from 7 months to 5 months• deleting 'pegylated interferon-based treatment' in the previous treatment for hepatitis C• deleting the trade name "Zometa®" to allow for the use of branded or generic ZA supplied for the study• permitting commercial, open-label IV bisphosphonates to be administered for hypercalcemia of malignancy, if necessary• clarifying that baseline tumor tissue can be submitted soon after randomization, and that samples should have ample tumor tissue• local laboratory tests (serum chemistry and complete blood count) can be from before each dosing visit, if per SOC• deaths that occur in survival follow-up will be reported to Amgen as serious adverse events• the criteria for authorship credit in a publication was updated per International Committee of Medical Journal Editor guidelines
22 April 2016	<ul style="list-style-type: none">• expanding primary endpoint to OS• evaluating "Tumor tissue RANK expression in correlation with OS" as a secondary endpoint• adding the opportunity for study subjects on regular assessments to obtain/remain on open-label denosumab should a positive benefit:risk profile be determined

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported