Clinical trial results:
A randomized, open-label, active-controlled, Phase II study of intravenous anetumab ravtansine (BAY 94-9343) or vinorelbine in patients with advanced or metastatic malignant pleural mesothelioma overexpressing mesothelin and progressed on first line platinum/pemetrexed-based chemotherapy

Summary

EudraCT number	2012-003650-88
Trial protocol	FI DE BE GB ES NL PL FR IT
Global end of trial date	06 September 2019

Results information

Result version number	v1 (current)
This version publication date	11 September 2020
First version publication date	11 September 2020

Trial information

Trial identification

Sponsor protocol code	BAY94-9343/15743

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02610140
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	06 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Superiority of anetumab ravtansine monotherapy over vinorelbine in progression-free survival (PFS)

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator:

Vinorelbine

Actual start date of recruitment	13 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Italy: 60
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United Kingdom: 44
Country: Number of subjects enrolled	United States: 23

Worldwide total number of subjects	248
EEA total number of subjects	197

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)	103
From 65 to 84 years	145
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Country / Number of study centers: Australia (5), Belgium (6), Canada (4), Finland (3), France (7), Italy (7), Republic of Korea (2), Netherlands (2), Poland (4), Russian Federation (2), Spain (5), Turkey (6), United Kingdom (7), and United States (16), between 03-Dec-2015 (first patient first visit) and 02-Jul-2019 (last patient last visit).

Pre-assignment

Screening details:

Overall, 589 patients were enrolled for pre-screening in the study (i.e., signed informed consent for pre-screening) and 274 patients were pre-screening failures. A total of 315 patients were screened; of these, 67 patients were screening failures.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Anetumab Ravtansine

Arm description:

Data cut-off date 06-APR-2018

Arm type	Experimental
Investigational medicinal product name	Anetumab ravtansine (BAY 94-9343)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

6.5 mg/kg every 3 weeks; Intravenous (IV) infusion over 1 hour

Arm title	Vinorelbine

Arm description:

Data cut-off date 06-APR-2018

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

Dosage and administration details:

30 mg/m^2 once weekly

Number of subjects in period 1	Anetumab Ravtansine	Vinorelbine
Started	166	82
Entered safety follow-up	102	45
Entered active follow-up	48	26
Entered long-term follow-up	123	66
Completed	0	0
Not completed	166	82
Study drug never administered	3	10
Discontinued study treatment	154	71
Ongoing with treatment but not completed	9	1

Baseline characteristics

Reporting groups	
Reporting group title	Anetumab Ravtansine
Reporting group description: Data cut-off date 06-APR-2018	
Reporting group title	Vinorelbine
Reporting group description: Data cut-off date 06-APR-2018	

Reporting group values	Anetumab Ravtansine	Vinorelbine	Total
Number of subjects	166	82	248
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	66	37	103
From 65-84 years	100	45	145
85 years and over	0	0	0
Age Continuous Units:			
	66.5 ± 42.0	65.5 ± 46.0	-
Gender Categorical Units: Subjects			
Female	44	20	64
Male	122	62	184

Subject analysis sets	
Subject analysis set title	Anetumab Ravtansine
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients were included in the Intent-to-treat set (ITT) set. Patients in this set were reported by treatment arm as randomized.	
Subject analysis set title	Vinorelbine
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients were included in the ITT set. Patients in this set were reported by treatment arm as randomized.	

Reporting group values	Anetumab Ravtansine	Vinorelbine	
Number of subjects	166	82	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	66	37	
From 65-84 years	100	45	
85 years and over	0	0	
Age Continuous Units:			
	66.5 ± 42.0	65.5 ± 46.0	
Gender Categorical Units: Subjects			
Female	44	20	
Male	122	62	

End points

End points reporting groups

Reporting group title	Anetumab Ravtansine
Reporting group description: Data cut-off date 06-APR-2018	
Reporting group title	Vinorelbine
Reporting group description: Data cut-off date 06-APR-2018	
Subject analysis set title	Anetumab Ravtansine
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients were included in the Intent-to-treat set (ITT) set. Patients in this set were reported by treatment arm as randomized.	
Subject analysis set title	Vinorelbine
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients were included in the ITT set. Patients in this set were reported by treatment arm as randomized.	

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description: Progression-free survival (PFS), defined as time from randomization until disease progression according to mRECIST (Modified Response Evaluation Criteria in Solid Tumors) for Malignant pleural mesothelioma (MPM) per blinded central radiology review, or death.	
End point type	Primary
End point timeframe: From randomization till approximately approx. 30 months (data cut-off: 31-May-2017) and 40 months (data cut-off: 06-Apr-2018)	

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: months				
median (confidence interval 95%)				
PFS - Data cut off: 31-May-2017 [95% CI]	4.3 (4.1 to 5.2)	4.5 (4.1 to 5.8)		
PFS - Data cut off: 06-Apr-2018 [95% CI]	4.3 (4.1 to 5.5)	4.6 (4.1 to 5.8)		
PFS - Data cut off: 31-May-2017 [97.5% CI]	4.3 (4.1 to 5.2)	4.5 (3.9 to 5.8)		
PFS - Data cut off: 06-Apr-2018[97.5% CI]	4.3 (4.1 to 5.6)	4.6 (3.9 to 5.8)		

Statistical analyses

Statistical analysis title	PFS - Data cut off: 31-May-2017
Statistical analysis description:	
Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.	
Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.859125 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.215
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.738

Notes:

[1] - 1-sided p-value from log-rank test (stratified by TTP on 1st line treatment). P-value is calculated based on alpha
level 0.0125.

Statistical analysis title	PFS - Data cut off: 06-Apr-2018
Statistical analysis description:	
Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.	
Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.121
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.813
upper limit	1.545

Statistical analysis title	PFS - Data cut off: 31-May-2017
Statistical analysis description:	
Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.	
Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	> 0.859125 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.215

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.807
upper limit	1.83

Notes:

[2] - 97.5% CIs correspond to 0.0125 one-sided alpha level.

[3] - 1-sided p-value from log-rank test (stratified by TTP on 1st line treatment). P-value is calculated based on alpha
level 0.0125.

Statistical analysis title	PFS - Data cut off: 06-Apr-2018

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority[4]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.121
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.776
upper limit	1.618

Notes:

[4] - 97.5% CIs correspond to 0.0125 one-sided alpha level.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS) was defined as time from randomization until death from any cause.

End point type	Secondary

End point timeframe:

Up to approx. 30 month (data cut-off: 31-May-2017) and (40 months (data cut-off: 06-Apr-2018) - Time from randomization until death from any cause; one-sided log-rank test stratified by time to progression (TTP) on first line treatment.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[5]	82		
Units: months				
median (confidence interval 95%)				
OS - Data cut off: 31-May-2017 [95% CI]	10.1 (7.6 to 99999.9)	11.6 (7.7 to 12.5)		
OS - Data cut off: 06-Apr-2018 [95% CI]	9.5 (8.3 to 12.3)	11.6 (8.6 to 13.1)		
OS - Data cut off: 31-May-2017 [adjusted CI%]	10.1 (7.0 to 99999.9)	11.6 (7.1 to 12.5)		

OS - Data cut off: 06-Apr-2018 [adjusted CI%]	9.5 (8.3 to 12.3)	11.6 (8.6 to 13.1)		

Notes:

[5] - OS - Data cut off: 31-May-2017 [CI]: 99999.9 = cannot be estimated due to censored data.

Statistical analyses

Statistical analysis title	OS - Data cut off: 31-May-2017

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.720888 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.724
upper limit	1.817

Notes:

[6] - 1-sided p-value from log-rank test (stratified by TTP on 1st line treatment). Alpha spending/boundary for interim
was 0.00245. Alpha boundary value for final analysis was 0.02421.

Statistical analysis title	OS - Data cut off: 06-Apr-2018

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.655624 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.763
upper limit	1.506

Notes:

[7] - 1-sided p-value from log-rank test (stratified by TTP on 1st line treatment). Alpha spending/boundary for interim
was 0.00245. Alpha boundary value for final analysis was 0.02421.

Statistical analysis title	OS - Data cut off: 31-May-2017

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	> 0.720888 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.147
Confidence interval	
level	Other: 99.51 %
sides	2-sided
lower limit	0.593
upper limit	2.221

Notes:

[8] - Interim analysis: CI adjusted for group sequential design: alpha spending for interim was 0.00245. The 99.51%
CIs are based on this adjusted alpha level. Final analysis: CI adjusted for group sequential design: Alpha spending for interim OS analysis was 0.00245. Final alpha level is 0.02421. The 95.158% CIs are based on
this adjusted alpha level.
[9] - 1-sided p-value from log-rank test (stratified by TTP on 1st line treatment). Alpha spending/boundary for interim
was 0.00245. Alpha boundary value for final analysis was 0.02421.

Statistical analysis title	OS - Data cut off: 06-Apr-2018

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	> 0.655624 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.072
Confidence interval	
level	95.16 %
sides	2-sided
lower limit	0.761
upper limit	1.51

Notes:

[10] - Interim analysis: CI adjusted for group sequential design: alpha spending for interim was 0.00245. The 99.51%
CIs are based on this adjusted alpha level. Final analysis: CI adjusted for group sequential design: Alpha spending for interim OS analysis was 0.00245. Final alpha level is 0.02421. The 95.158% CIs are based on
this adjusted alpha level.
[11] - 1-sided p-value from log-rank test (stratified by TTP on 1st line treatment). Alpha spending/boundary for interim
was 0.00245. Alpha boundary value for final analysis was 0.02421.

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

A patient is a responder if the patient has a confirmed best tumor response on-study of CR (Complete response) or PR (Partial response), as determined by the central radiological reviewer per mRECIST criteria. ORR in each treatment arm was defined as the number of responders divided by the number of randomized patients. A responder was a patient who had a confirmed best tumor response on-study of CR or PR, as determined by the central radiological reviewer per mRECIST criteria.

End point type	Secondary

End point timeframe:

up to approx. 30 months (data cut-off: 31-May-2017) and 40 months (data cut-off: 06-Apr-2018) - Time from randomization until death from any cause.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Percentage				
number (confidence interval 95%)				
ORR: Data cut off 31-May-2017	8.4 (4.7 to 13.7)	6.1 (2.0 to 13.7)		
ORR: Data cut off 06-Apr-2018	9.6 (5.6 to 15.2)	7.3 (2.7 to 15.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

A patient has disease control if the patient has a best tumor response on-study of CR, PR, or SD (Stable disease). DCR was defined as a percentage of patients achieving CR, PR, or SD per mRECIST criteria, as determined by the central radiological reviewer. DCR was calculated in each treatment arm as the number of patients with disease control (a best tumor response on-study of CR, PR, or SD) divided by the number of randomized patients.

End point type	Secondary

End point timeframe:

Up to approx. 30 months (data cut-off: 31-May-2017) and 40 months (data cut-off: 06-Apr-2018) - Time from randomization until death from any cause.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Percentage				
number (confidence interval 95%)				
DCR - Data cut off: 31- May-2017	73.5 (66.1 to 80.0)	68.3 (57.1 to 78.1)		

DCR - Data cut off: 06-Apr- 2018	73.5 (66.1 to 80.0)	68.3 (57.1 to 78.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

DOR was defined in responders as the time from central documentation of tumor response (date of first response in the confirmation sequence) to the earlier of disease progression as determined by the central radiological reviewer, or death without centrally documented progression. A responder was a patient who had a confirmed best tumor response on-study of CR or PR, as determined by the central radiological reviewer per mRECIST criteria.

End point type	Secondary

End point timeframe:

Up to approx. 30 months (data cut-off: 31-May-2017) and 40 months (data cut-off: 06-Apr-2018) - Time from randomization until death from any cause.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[12]	82[13]		
Units: months				
median (confidence interval 95%)				
DOR - Data cut off: 31- May-2017	6.5 (4.6 to 9999.9)	3333.3 (3.1 to 9999.9)		
DOR - Data cut off: 06-Apr- 2018	7.4 (6.0 to 9999.9)	6.7 (3.0 to 10.3)		

Notes:

[12] - 99999.9 = CI limit values could not be estimated due to censored data.

[13] - 3333.3 / 99999.9 = CI limit values could not be estimated due to censored data.

Statistical analyses

No statistical analyses for this end point

Secondary: Durable response rate (DRR)

End point title	Durable response rate (DRR)

End point description:

A durable responder was a responder (i.e. confirmed best tumor response on study of CR or PR) with duration of response of 180 days or more.

End point type	Secondary

End point timeframe:

Up to approx. 30 months (data cut-off: 31-May-2017) and 40 months (data cut-off: 06-Apr-2018) - Time from randomization until death from any cause.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Percentage				
number (confidence interval 95%)				
DRR: Data cut off 31- May-2017	4.2 (1.7 to 8.5)	1.2 (0.0 to 6.6)		
ORR: Data cut off 06- Apr-2018	7.2 (3.8 to 12.3)	4.9 (1.3 to 12.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Confirmed Improvement of Symptoms Characteristic of Mesothelioma

End point title	Percentage of Participants With Confirmed Improvement of Symptoms Characteristic of Mesothelioma

End point description:

Improvement rate of symptoms characteristic of mesothelioma was defined as the number of patients with confirmed improvement of symptoms characteristic of mesothelioma (based on the MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma, MDASI-MPM), divided by the number of patients evaluable for improvement of symptoms characteristic of mesothelioma.

End point type	Secondary

End point timeframe:

up to approx. 30 months (data cut-off: 31-May-2017) and 40 months (data cut-off: 06-Apr-2018)

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[14]	82[15]		
Units: days				
median (confidence interval 95%)				
TTWS: Data cut off 31- May-2017	3333.3 (1111.1 to 9999.9)	3333.3 (1111.1 to 9999.9)		
TTWS: Data cut off 06- Apr-2018	3333.3 (1111.1 to 9999.9)	3333.3 (291.0 to 9999.9)		

Notes:

[14] - 1111.1, 3333.3, 9999.9 = CI limit values could not be estimated due to censored data.

[15] - 1111.1, 3333.3, 9999.9 = CI limit values could not be estimated due to censored data.

Statistical analyses

Statistical analysis title	TTWS - Data cut off 31-May-2017

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.313747 [16]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.829
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.386
upper limit	1.779

Notes:

[16] - 1-sided p-value from log-rank test (stratified by TTP on 1st line treatment).

Statistical analysis title	TTWS - Data cut off 06-Apr-2018

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.971
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.479
upper limit	1.968

Secondary: Time to worsening of pain (TTWP)

End point title	Time to worsening of pain (TTWP)

End point description:

Time to worsening of pain (TTWP) was defined in patients evaluable for assessing worsening of pain, as time from randomization until the first worsening of pain. Patients who died, were lost to follow-up, or ended (MD Anderson Symptom Inventory-Malignant Pleural Mesothelioma) MDASI-MPM assessments without confirmed worsening of pain were censored at the date of their last MDASI-MPM assessment with a non-missing pain score.

End point type	Secondary

End point timeframe:

up to approx. 30 months (data cut-off: 31-May-2017) and 40 months (data cut-off: 06-Apr-2018)

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[17]	82[18]		
Units: days				
median (confidence interval 95%)				
TTWP: Data cut off 31- May-2017	210.0 (127.0 to 9999.9)	3333.3 (85.0 to 9999.9)		
TTWP: Data cut off 06- Apr-2018	210.0 (127.0 to 9999.9)	3333.3 (85.0 to 9999.9)		

Notes:

[17] - 3333.3, 9999.9 = CI limit values could not be estimated due to censored data.

[18] - 3333.3, 9999.9 = CI limit values could not be estimated due to censored data.

Statistical analyses

Statistical analysis title	TTWP - Data cut off 31-May-2017

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.378916 [19]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.924
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.557
upper limit	1.533

Notes:

[19] - 1-sided p-value from log-rank test (stratified by TTP on 1st line treatment).

Statistical analysis title	TTWP - Data cut off 06-Apr-2018

Statistical analysis description:

Hazard ratio (anetumab ravtansine/vinorelbine) was estimated using Cox proportional hazards models with Wald CIs, stratified by TTP on 1st line treatment.

Comparison groups	Anetumab Ravtansine v Vinorelbine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.903

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.546
upper limit	1.495

Secondary: Improvement rate of symptoms characteristic of mesothelioma

End point title	Improvement rate of symptoms characteristic of mesothelioma

End point description:

Improvement rate of symptoms characteristic of mesothelioma was defined as the number of patients with confirmed improvement of symptoms characteristic of mesothelioma (based on the MDASI-MPM), divided by the number of patients evaluable for improvement of symptoms characteristic of mesothelioma. Confirmation of this endpoint required two consecutive MDASI-MPM assessments with improved symptoms, with no more than one missing CSS assessment in between.

End point type	Secondary

End point timeframe:

Time from randomization until death from any cause.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Percentage				
number (confidence interval 95%)				
Data cut off 31-May-2017	22.5 (15.1 to 31.4)	17.9 (8.9 to 30.4)		
Data cut off 06-Apr-2018	23.4 (15.9 to 32.4)	19.6 (10.2 to 32.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Confirmed Improvement of Pain

End point title	Percentage of Participants With Confirmed Improvement of Pain

End point description:

Improvement rate of pain was defined as the number of patients with confirmed improvement of pain (based on the "pain at its worst" item of MDASI-MPM), divided by the number of patients evaluable for improvement of pain.

End point type	Secondary

End point timeframe:

Up to approx. 30 months (data cut-off: 31-May-2017) and 40 months (data cut-off: 06-Apr-2018) - Time from randomization until death from any cause.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Percentage				
number (confidence interval 95%)				
Data cut off 31-May-2017	39.4 (30.0 to 49.5)	32.7 (19.9 to 47.5)		
Data cut off 06-Apr-2018	40.4 (30.9 to 50.5)	32.7 (19.9 to 47.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) - Addendum

End point title	Overall survival (OS) - Addendum

End point description:

Overall survival (OS) was defined as time from randomization until death from any cause.

End point type	Secondary

End point timeframe:

Up to approx. 55 month (data cut-off: 02-JUL-2019) - Time from randomization until death from any cause; one-sided log-rank test stratified by time to progression (TTP) on first line treatment.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[20]	82[21]		
Units: month				
median (confidence interval 95%)				
OS (months)	9.5 (8.3 to 12.3)	11.6 (8.6 to 13.1)		

Notes:

[20] - Number of patients with death from any cause: 127
Number of patients with censored observation 39

[21] - Number of patients with death from any cause: 59
Number of patients with censored observation 23

Statistical analyses

Statistical analysis title	OS - Data cut off: 02-Jul-2019

Statistical analysis description:

Range (including censored values)

Comparison groups	Anetumab Ravtansine v Vinorelbine

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Range (including censored values)
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	39.3

Statistical analysis title	OS - Data cut off: 02-Jul-2019
Statistical analysis description:	
Range (including censored values)	
Comparison groups	Vinorelbine v Anetumab Ravtansine
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Range (including censored values)
Point estimate	11.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	35.9

Secondary: Percentage of Participant With Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Participant With Treatment-emergent Adverse Events (TEAEs)

End point description:

TEAEs = Treatment-emergent adverse events / TESAEs = Treatment-emergent serious adverse events were defined as all AEs (adverse events) / SAEs (serious adverse events) starting or worsening within the treatment period. The treatment period for this study extended from the initiation of study treatment until 30 days after the last administration of study treatment.

End point type	Secondary

End point timeframe:

Up to approx. 30 months (data cut-off: 31-May-2017), 40 months (data cut-off: 06-Apr-2018) and 55 months (data cut-off: 02-Jul-2019)

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	72		
Units: Percentage				
number (not applicable)				
Data cut-off: 31-May-2017: Any TEAE	99.4	98.6		
Data cut-off: 31-May-2017: TESAE	31.9	34.7		
Data cut-off: 31-May-2017: Drug-related TEAE	87.7	90.3		
Data cut-off: 31-May-2017: Drug-related TESAE	38.7	70.8		
Data cut-off: 06-Apr-2018: Any TEAE	99.4	98.6		
Data cut-off: 06-Apr-2018: TESAE	33.7	34.7		
Data cut-off: 06-Apr-2018: Drug-related TEAE	87.7	90.3		
Data cut-off: 06-Apr-2018: Drug-related TESAE	39.9	70.8		
Data cut-off: 02-Jul-2019: Any TEAE	99.4	98.6		
Data cut-off: 02-Jul-2019: TESAE	34.4	34.7		
Data cut-off: 02-Jul-2019: Drug-related TEAE	88.3	90.3		
Data cut-off: 02-Jul-2019: Drug-related TESAE	7.4	15.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Deaths

End point title	Number of Deaths

End point description:

TEAE(s) associated with a fatal outcome (CTCAE Grade 5); Table contains deaths only if due to a TEAE. TEAEs were defined as all AEs starting or worsening within the treatment period. The treatment period for this study, for purposes of safety analyses, extended from the initiation of study treatment until 30 days after the last administration of study treatment.

End point type	Secondary

End point timeframe:

Up to approx. 30 months (data cut-off: 31-May-2017), 40 months (data cut-off: 06-Apr-2018) and 55 months (data cut-off: 02-Jul-2019) - Time from randomization until death from any cause.

End point values	Anetumab Ravtansine	Vinorelbine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	72		
Units: Number				
Data cut-off: 31-May-2017	9	1		
Data cut-off: 06-Apr-2018	10	1		
Data cut-off: 02-Jul-2019	10	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

FPFV: 03-Dec-2015 until LPLV: 02-Jul-2019

Adverse event reporting additional description:

TEAEs = Treatment-emergent adverse events were defined as all AEs starting or worsening within the treatment period. The treatment period for this study extended from the initiation of study treatment until 30 days after the last administration of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Vinorelbine

Reporting group description:

Treatment-emergent adverse events (TEAEs): defined as all AEs starting or worsening within the treatment period.

Reporting group title	Anetumab ravtansine (BAY 94-9343)

Reporting group description:

Treatment-emergent adverse events (TEAEs): defined as all AEs starting or worsening within the treatment period.

Serious adverse events	Vinorelbine	Anetumab ravtansine (BAY 94-9343)	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 72 (34.72%)	56 / 163 (34.36%)	
number of deaths (all causes)	55	126	
number of deaths resulting from adverse events	1	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mesothelioma			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cancer pain			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour compression			

subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 72 (4.17%)	3 / 163 (1.84%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	

Physical deconditioning			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Scrotal mass			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 72 (2.78%)	7 / 163 (4.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dyspnoea exertional			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
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	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 72 (2.78%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			

subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial flutter			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Loss of consciousness			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexopathy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 72 (4.17%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	2 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 72 (1.39%)	5 / 163 (3.07%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			

subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (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	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute kidney injury			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (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			
Abscess			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	5 / 72 (6.94%)	7 / 163 (4.29%)	
occurrences causally related to treatment / all	3 / 6	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 3	
Sepsis			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Upper respiratory tract infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 72 (2.78%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Vinorelbine	Anetumab ravtansine (BAY 94-9343)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 72 (98.61%)	162 / 163 (99.39%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Cancer pain			
subjects affected / exposed	1 / 72 (1.39%)	5 / 163 (3.07%)	
occurrences (all)	1	7	
Tumour pain			
subjects affected / exposed	3 / 72 (4.17%)	2 / 163 (1.23%)	
occurrences (all)	3	2	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	2 / 72 (2.78%)	9 / 163 (5.52%)	
occurrences (all)	5	13	
Hypotension			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	2	
Jugular vein thrombosis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Peripheral coldness			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	6 / 72 (8.33%)	0 / 163 (0.00%)	
occurrences (all)	9	0	
Raynaud's phenomenon			

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Deep vein thrombosis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Vascular pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Superior vena cava occlusion			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Hot flush			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Embolism			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Dermabrasion			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Inguinal hernia repair			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Application site rash			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	16 / 72 (22.22%)	32 / 163 (19.63%)	
occurrences (all)	37	58	
Chest discomfort			
subjects affected / exposed	3 / 72 (4.17%)	4 / 163 (2.45%)	
occurrences (all)	3	6	
Chest pain			

subjects affected / exposed	13 / 72 (18.06%)	27 / 163 (16.56%)	
occurrences (all)	21	31	
Chills			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	22 / 72 (30.56%)	60 / 163 (36.81%)	
occurrences (all)	47	98	
Feeling cold			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			
subjects affected / exposed	0 / 72 (0.00%)	4 / 163 (2.45%)	
occurrences (all)	0	4	
Hyperpyrexia			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	2	
Influenza like illness			
subjects affected / exposed	5 / 72 (6.94%)	5 / 163 (3.07%)	
occurrences (all)	9	8	
Injection site bruising			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	5 / 72 (6.94%)	8 / 163 (4.91%)	
occurrences (all)	5	13	
Mass			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	3 / 72 (4.17%)	2 / 163 (1.23%)	
occurrences (all)	3	2	
Oedema			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Oedema peripheral			

subjects affected / exposed	3 / 72 (4.17%)	11 / 163 (6.75%)	
occurrences (all)	4	11	
Pyrexia			
subjects affected / exposed	12 / 72 (16.67%)	22 / 163 (13.50%)	
occurrences (all)	14	25	
Pain			
subjects affected / exposed	1 / 72 (1.39%)	4 / 163 (2.45%)	
occurrences (all)	1	5	
Peripheral swelling			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	4	
Infusion site pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Infusion site swelling			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Inflammation			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	3 / 72 (4.17%)	7 / 163 (4.29%)	
occurrences (all)	3	10	
Infusion site extravasation			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Catheter site injury			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	

Contrast media allergy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Breast pain			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Scrotal mass			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Penile oedema			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 72 (15.28%)	22 / 163 (13.50%)	
occurrences (all)	15	30	
Dysphonia			
subjects affected / exposed	3 / 72 (4.17%)	2 / 163 (1.23%)	
occurrences (all)	3	2	
Epistaxis			
subjects affected / exposed	1 / 72 (1.39%)	9 / 163 (5.52%)	
occurrences (all)	1	12	
Dyspnoea			
subjects affected / exposed	20 / 72 (27.78%)	30 / 163 (18.40%)	
occurrences (all)	26	44	
Dyspnoea exertional			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	4	
Haemoptysis			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Hiccups			

subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Nasal dryness			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	1 / 72 (1.39%)	3 / 163 (1.84%)	
occurrences (all)	1	5	
Painful respiration			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Pleuritic pain			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Pneumonitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	4	0	
Pneumothorax			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 72 (1.39%)	3 / 163 (1.84%)	
occurrences (all)	1	3	
Pulmonary embolism			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	2	
Rhinorrhoea			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Diaphragmalgia			

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Increased upper airway secretion			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Increased viscosity of bronchial secretion			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 72 (4.17%)	4 / 163 (2.45%)	
occurrences (all)	3	4	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	3 / 72 (4.17%)	5 / 163 (3.07%)	
occurrences (all)	3	9	
Confusional state			
subjects affected / exposed	0 / 72 (0.00%)	4 / 163 (2.45%)	
occurrences (all)	0	4	
Depression			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	1	2	
Depressed mood			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Enuresis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Insomnia			

subjects affected / exposed	10 / 72 (13.89%)	11 / 163 (6.75%)	
occurrences (all)	10	13	
Sleep disorder			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Device occlusion			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	6 / 72 (8.33%)	20 / 163 (12.27%)	
occurrences (all)	10	46	
Amylase increased			
subjects affected / exposed	1 / 72 (1.39%)	5 / 163 (3.07%)	
occurrences (all)	1	11	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 72 (5.56%)	22 / 163 (13.50%)	
occurrences (all)	4	43	
Bilirubin conjugated increased			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Blood albumin decreased			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	3	
Blood creatinine increased			
subjects affected / exposed	1 / 72 (1.39%)	4 / 163 (2.45%)	
occurrences (all)	1	5	
Blood bilirubin increased			

subjects affected / exposed	2 / 72 (2.78%)	3 / 163 (1.84%)		
occurrences (all)	2	5		
Blood lactic acid increased				
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)		
occurrences (all)	1	0		
C-reactive protein increased				
subjects affected / exposed	2 / 72 (2.78%)	3 / 163 (1.84%)		
occurrences (all)	2	4		
Blood urea increased				
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)		
occurrences (all)	0	2		
Blood pressure increased				
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)		
occurrences (all)	0	1		
Electrocardiogram QT prolonged				
subjects affected / exposed	2 / 72 (2.78%)	5 / 163 (3.07%)		
occurrences (all)	3	5		
Gamma-glutamyltransferase increased				
subjects affected / exposed	3 / 72 (4.17%)	11 / 163 (6.75%)		
occurrences (all)	5	24		
Glucose tolerance test abnormal				
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)		
occurrences (all)	0	1		
Haemoglobin decreased				
subjects affected / exposed	3 / 72 (4.17%)	2 / 163 (1.23%)		
occurrences (all)	5	2		
Lipase increased				
subjects affected / exposed	1 / 72 (1.39%)	7 / 163 (4.29%)		
occurrences (all)	1	17		
Lymphocyte count decreased				
subjects affected / exposed	2 / 72 (2.78%)	1 / 163 (0.61%)		
occurrences (all)	5	1		
Neutrophil count decreased				
subjects affected / exposed	17 / 72 (23.61%)	3 / 163 (1.84%)		
occurrences (all)	41	5		

Platelet count decreased				
subjects affected / exposed	0 / 72 (0.00%)	4 / 163 (2.45%)		
occurrences (all)	0	11		
Weight decreased				
subjects affected / exposed	8 / 72 (11.11%)	17 / 163 (10.43%)		
occurrences (all)	12	23		
White blood cell count decreased				
subjects affected / exposed	9 / 72 (12.50%)	2 / 163 (1.23%)		
occurrences (all)	25	3		
White blood cell count increased				
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)		
occurrences (all)	0	1		
Blood phosphorus decreased				
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)		
occurrences (all)	1	0		
Blood phosphorus increased				
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)		
occurrences (all)	0	1		
Hypophonesis				
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)		
occurrences (all)	1	0		
Platelet count increased				
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)		
occurrences (all)	0	1		
Transaminases increased				
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)		
occurrences (all)	0	1		
Blood alkaline phosphatase increased				
subjects affected / exposed	0 / 72 (0.00%)	4 / 163 (2.45%)		
occurrences (all)	0	4		
Klebsiella test positive				
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)		
occurrences (all)	0	1		
Blood creatine phosphokinase decreased				

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Waist circumference increased			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Tear break up time decreased			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Clavicle fracture			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	2 / 72 (2.78%)	3 / 163 (1.84%)	
occurrences (all)	2	3	
Ligament sprain			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Scratch			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Muscle strain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction			
subjects affected / exposed	4 / 72 (5.56%)	16 / 163 (9.82%)	
occurrences (all)	4	22	
Stoma site pain			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	2	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 72 (1.39%)	3 / 163 (1.84%)	
occurrences (all)	1	3	
Atrial flutter			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Bundle branch block left			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	2	0	
Atrial tachycardia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 72 (1.39%)	3 / 163 (1.84%)	
occurrences (all)	1	3	
Coronary artery occlusion			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	2	2	
Sinus tachycardia			
subjects affected / exposed	1 / 72 (1.39%)	5 / 163 (3.07%)	
occurrences (all)	1	6	
Tachycardia			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	1	2	
Nervous system disorders			
Asterixis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Ageusia			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Dizziness			

subjects affected / exposed	6 / 72 (8.33%)	6 / 163 (3.68%)	
occurrences (all)	6	6	
Burning sensation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Dizziness postural			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Dysaesthesia			
subjects affected / exposed	0 / 72 (0.00%)	5 / 163 (3.07%)	
occurrences (all)	0	11	
Dysgeusia			
subjects affected / exposed	1 / 72 (1.39%)	7 / 163 (4.29%)	
occurrences (all)	1	9	
Dysarthria			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Dyskinesia			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	5 / 72 (6.94%)	15 / 163 (9.20%)	
occurrences (all)	8	17	
Lethargy			
subjects affected / exposed	5 / 72 (6.94%)	4 / 163 (2.45%)	
occurrences (all)	12	9	
Hypoaesthesia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	2	
Neuralgia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	5 / 72 (6.94%)	27 / 163 (16.56%)	
occurrences (all)	6	52	
Neurotoxicity			

subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	5 / 72 (6.94%)	14 / 163 (8.59%)	
occurrences (all)	7	44	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 72 (0.00%)	20 / 163 (12.27%)	
occurrences (all)	0	44	
Polyneuropathy			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	8	
Sciatica			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	7	
Syncope			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Balance disorder			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Brachial plexopathy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Taste disorder			

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 72 (27.78%)	15 / 163 (9.20%)	
occurrences (all)	42	25	
Febrile neutropenia			
subjects affected / exposed	3 / 72 (4.17%)	0 / 163 (0.00%)	
occurrences (all)	3	0	
Neutropenia			
subjects affected / exposed	35 / 72 (48.61%)	3 / 163 (1.84%)	
occurrences (all)	80	4	
Leukopenia			
subjects affected / exposed	5 / 72 (6.94%)	2 / 163 (1.23%)	
occurrences (all)	12	2	
Thrombocytosis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 72 (0.00%)	8 / 163 (4.91%)	
occurrences (all)	0	13	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Vertigo			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Hypoacusis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Excessive cerumen production			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Eye disorders			

Cataract			
subjects affected / exposed	2 / 72 (2.78%)	9 / 163 (5.52%)	
occurrences (all)	2	13	
Blepharitis			
subjects affected / exposed	0 / 72 (0.00%)	5 / 163 (3.07%)	
occurrences (all)	0	5	
Cataract cortical			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Corneal erosion			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	2	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Cataract nuclear			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Diplopia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 72 (0.00%)	22 / 163 (13.50%)	
occurrences (all)	0	26	
Eye irritation			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Eye discharge			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Lacrimation decreased			
subjects affected / exposed	0 / 72 (0.00%)	6 / 163 (3.68%)	
occurrences (all)	0	7	
Eye pain			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	3	

Lacrimation disorder			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Ocular hypertension			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Photophobia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Pinguecula			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Retinal haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Retinal tear			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 72 (0.00%)	5 / 163 (3.07%)	
occurrences (all)	0	6	
Retinal vascular disorder			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	0 / 72 (0.00%)	6 / 163 (3.68%)	
occurrences (all)	0	7	
Visual impairment			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Vitreous floaters			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	

Conjunctival hyperaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Eye pruritus			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Ocular discomfort			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Corneal disorder			
subjects affected / exposed	0 / 72 (0.00%)	65 / 163 (39.88%)	
occurrences (all)	0	156	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 72 (5.56%)	4 / 163 (2.45%)	
occurrences (all)	4	4	
Abdominal pain			
subjects affected / exposed	10 / 72 (13.89%)	18 / 163 (11.04%)	
occurrences (all)	13	27	
Abdominal pain lower			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	5 / 72 (6.94%)	9 / 163 (5.52%)	
occurrences (all)	5	14	
Ascites			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	5	
Aphthous ulcer			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	34 / 72 (47.22%)	29 / 163 (17.79%)	
occurrences (all)	51	39	
Diarrhoea			

subjects affected / exposed	15 / 72 (20.83%)	56 / 163 (34.36%)	
occurrences (all)	22	91	
Dry mouth			
subjects affected / exposed	0 / 72 (0.00%)	7 / 163 (4.29%)	
occurrences (all)	0	8	
Dyspepsia			
subjects affected / exposed	1 / 72 (1.39%)	13 / 163 (7.98%)	
occurrences (all)	1	14	
Dysphagia			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	1	4	
Flatulence			
subjects affected / exposed	1 / 72 (1.39%)	4 / 163 (2.45%)	
occurrences (all)	1	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 72 (1.39%)	6 / 163 (3.68%)	
occurrences (all)	1	7	
Gastrointestinal disorder			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Gingival bleeding			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	2	
Glossitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	2 / 72 (2.78%)	1 / 163 (0.61%)	
occurrences (all)	2	1	
Inguinal hernia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Lip oedema			

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	24 / 72 (33.33%)	68 / 163 (41.72%)	
occurrences (all)	38	130	
Oral pain			
subjects affected / exposed	3 / 72 (4.17%)	0 / 163 (0.00%)	
occurrences (all)	3	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Stomatitis			
subjects affected / exposed	5 / 72 (6.94%)	2 / 163 (1.23%)	
occurrences (all)	6	2	
Vomiting			
subjects affected / exposed	5 / 72 (6.94%)	34 / 163 (20.86%)	
occurrences (all)	8	62	
Aerophagia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Paraesthesia oral			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Hepatocellular injury			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	

Jaundice cholestatic			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 72 (2.78%)	3 / 163 (1.84%)	
occurrences (all)	2	3	
Dermatitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Dermatitis acneiform			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	4	
Erythema multiforme			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 72 (1.39%)	5 / 163 (3.07%)	
occurrences (all)	1	5	
Hyperkeratosis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Ingrowing nail			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Nail disorder			

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	2 / 72 (2.78%)	7 / 163 (4.29%)	
occurrences (all)	2	9	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	5	
Psoriasis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	3 / 72 (4.17%)	9 / 163 (5.52%)	
occurrences (all)	3	12	
Rash macular			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Rash papular			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	4	
Rash pruritic			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Skin irritation			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	

Skin hypertrophy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Pruritus generalised			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	1	2	
Nocturia			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Proteinuria			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Urinary tract pain			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Bladder trabeculation			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Acute kidney injury			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 72 (4.17%)	19 / 163 (11.66%)	
occurrences (all)	3	29	
Back pain			
subjects affected / exposed	9 / 72 (12.50%)	11 / 163 (6.75%)	
occurrences (all)	10	13	
Coccydynia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Flank pain			
subjects affected / exposed	2 / 72 (2.78%)	1 / 163 (0.61%)	
occurrences (all)	3	1	
Joint swelling			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Muscle discomfort			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	3 / 72 (4.17%)	8 / 163 (4.91%)	
occurrences (all)	3	8	
Muscular weakness			
subjects affected / exposed	2 / 72 (2.78%)	6 / 163 (3.68%)	
occurrences (all)	2	7	
Musculoskeletal pain			
subjects affected / exposed	3 / 72 (4.17%)	10 / 163 (6.13%)	
occurrences (all)	3	13	
Myalgia			
subjects affected / exposed	5 / 72 (6.94%)	22 / 163 (13.50%)	
occurrences (all)	7	34	
Myopathy			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	

Neck pain			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	3	
Pain in extremity			
subjects affected / exposed	4 / 72 (5.56%)	10 / 163 (6.13%)	
occurrences (all)	5	11	
Pain in jaw			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Rotator cuff syndrome			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 72 (2.78%)	9 / 163 (5.52%)	
occurrences (all)	3	13	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Muscle contracture			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	2	
Tendon pain			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 72 (4.17%)	4 / 163 (2.45%)	
occurrences (all)	4	5	
Cellulitis			

subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	3	
Conjunctivitis			
subjects affected / exposed	1 / 72 (1.39%)	3 / 163 (1.84%)	
occurrences (all)	1	4	
Cystitis			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Eyelid infection			
subjects affected / exposed	1 / 72 (1.39%)	1 / 163 (0.61%)	
occurrences (all)	1	1	
Eye infection			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	3	
Ear infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Gastrointestinal infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Genital candidiasis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	2	
Lower respiratory tract infection			
subjects affected / exposed	2 / 72 (2.78%)	0 / 163 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			

subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Oral candidiasis			
subjects affected / exposed	4 / 72 (5.56%)	5 / 163 (3.07%)	
occurrences (all)	4	5	
Otitis media			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	3 / 72 (4.17%)	2 / 163 (1.23%)	
occurrences (all)	3	3	
Sinusitis			
subjects affected / exposed	2 / 72 (2.78%)	1 / 163 (0.61%)	
occurrences (all)	2	1	
Tonsillitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	5 / 72 (6.94%)	5 / 163 (3.07%)	
occurrences (all)	8	7	
Urinary tract infection			
subjects affected / exposed	0 / 72 (0.00%)	7 / 163 (4.29%)	
occurrences (all)	0	9	
Rectal abscess			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	5	
Vaginal infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Febrile infection			

subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	1	2	
Oral fungal infection			
subjects affected / exposed	0 / 72 (0.00%)	2 / 163 (1.23%)	
occurrences (all)	0	2	
Bronchitis bacterial			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Penile infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	1	2	
Lip infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Mucosal infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Peripheral nerve infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Infectious pleural effusion			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	3	
Candida infection			
subjects affected / exposed	2 / 72 (2.78%)	1 / 163 (0.61%)	
occurrences (all)	2	1	
Tongue fungal infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 163 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Folate deficiency			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	0 / 72 (0.00%)	3 / 163 (1.84%)	
occurrences (all)	0	3	
Hyperglycaemia			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	2	3	
Hyperkalaemia			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	1	3	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 163 (0.61%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	1 / 72 (1.39%)	2 / 163 (1.23%)	
occurrences (all)	1	3	
Hypoalbuminaemia			
subjects affected / exposed	4 / 72 (5.56%)	1 / 163 (0.61%)	
occurrences (all)	5	1	
Hypocalcaemia			
subjects affected / exposed	2 / 72 (2.78%)	1 / 163 (0.61%)	
occurrences (all)	6	1	
Hypokalaemia			
subjects affected / exposed	2 / 72 (2.78%)	7 / 163 (4.29%)	
occurrences (all)	9	8	
Hyponatraemia			
subjects affected / exposed	2 / 72 (2.78%)	3 / 163 (1.84%)	
occurrences (all)	2	5	
Hypomagnesaemia			
subjects affected / exposed	2 / 72 (2.78%)	1 / 163 (0.61%)	
occurrences (all)	2	1	
Hypophosphataemia			
subjects affected / exposed	3 / 72 (4.17%)	1 / 163 (0.61%)	
occurrences (all)	5	1	

Decreased appetite subjects affected / exposed occurrences (all)	17 / 72 (23.61%) 24	58 / 163 (35.58%) 75	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2016	1. The study design was changed to increase the power of the OS analysis with a corresponding increase in sample size and an increase in number of required OS events. 2. Information was updated on the estimated number of prescreened and screened patients needed to reach 210 randomized patients. The revised design also incorporated assumptions changes, including an increase in the accrual rate, more conservative PFS dropout assumptions, and a lower OS dropout assumption.
11 August 2016	1 The option for 5 drug half lives was removed from the time window for prior treatment with platinum in combination with pemetrexed before the start of study treatment. 2. Exclusion of patients having received prior device therapy. 3. Exclusion of patients with central nervous system metastasis. 4. DRR was added as a secondary variable. 5. Final analyses of DOR and DRR were specified to occur at the time of final OS analysis.
18 April 2017	1. Dextrose was added as an alternative diluent for anetumab ravtansine.
27 March 2018	1. Following OS data maturation, patients remaining on study will continue to be followed with reduced mandated assessments and data collection. in anetumab ravtansine and vinorelbine arms, respectively. 2. The sponsor will continue to assess survival data on patients after OS data maturation until 24 months after last patient's last treatment. 3. Clarification that end of study is defined by last visit of the last patient within the 15743 study and as a whole the date when the final clean database is available. In addition the possibility that treatment or follow up of subjects could continue within a separate program was included. 4. Allow delay in administration of anetumab ravtansine for up to 12 weeks and patients should be allowed to continue as per investigator's discretion if they are benefitting from treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported