Clinical trial results:
Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy (LUME Lung 1).

Summary

EudraCT number	2007-004803-36
Trial protocol	DE BE CZ AT DK LT ES SK GB FR PT BG IT GR
Global end of trial date	13 November 2017

Results information

Result version number	v2 (current)
This version publication date	14 November 2021
First version publication date	25 November 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1199.13

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	11 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 November 2010
Global end of trial reached?	Yes
Global end of trial date	13 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of nintedanib as compared to matching placebo in patients with stage IIIB/IV or recurrent non small cell lung cancer (NSCLC) treated with standard therapy of docetaxel after failure of first line chemotherapy

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 224
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	India: 158
Country: Number of subjects enrolled	South Africa: 43
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Bulgaria: 37
Country: Number of subjects enrolled	Belarus: 53
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Germany: 204
Country: Number of subjects enrolled	Denmark: 22
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Georgia: 35
Country: Number of subjects enrolled	Greece: 35
Country: Number of subjects enrolled	Croatia: 12
Country: Number of subjects enrolled	Italy: 42
Country: Number of subjects enrolled	Israel: 48
Country: Number of subjects enrolled	Lithuania: 20

Country: Number of subjects enrolled	Portugal: 44
Country: Number of subjects enrolled	Poland: 149
Country: Number of subjects enrolled	Russian Federation: 176
Country: Number of subjects enrolled	Romania: 105
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Ukraine: 177
Country: Number of subjects enrolled	United Kingdom: 19
Worldwide total number of subjects	1773
EEA total number of subjects	811

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)	1229
From 65 to 84 years	543
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Two-arm, randomised, double-blind, placebo-controlled, parallel-group comparison of nintedanib versus matching placebo. In this study,1773 subjects were enrolled, 1314 subjects were randomised and entered and 1307 subjects were treated.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial drug if any of the specific entry criteria was violated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The trial had a parallel-group, double-blind, placebo-controlled design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nintedanib plus docetaxel

Arm description:

Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 milligram (mg)/square meter (m2) once every 3 weeks administered via intravenous infusion over 1 hour (h).

Arm type	Experimental
Investigational medicinal product name	docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h) with dose reduction to 60 mg/m2 if required.

Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule with dose reduction to 150 mg b.i.d. or 100 mg twice daily (b.i.d.) (according to the protocol-defined dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

Arm title	Placebo plus docetaxel

Arm description:

Placebo soft gelatin capsule matching that of nintedanib 2 times daily plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).

Arm type	Placebo

Investigational medicinal product name	matching placebo to nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

matching placebo to nintedanib twice daily administered orally in a form of a soft gelatin capsule.

Investigational medicinal product name	docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h) with dose reduction to 60 mg/m2 if required.

Number of subjects in period 1[1]	Nintedanib plus docetaxel	Placebo plus docetaxel
Started	655	659
Completed	6	5
Not completed	649	654
Protocol deviation	9	9
Worsening or AE of underlying disease	64	70
Reasons other than stated above	20	16
Other AE - Non−Fatal event	54	50
Other AE - Fatal event	30	23
Consent withdrawn by subject	60	42
Progressive disease (modified RECIST)	404	435
Not treated	3	4
Lost to follow-up	5	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all enrolled subjects were randomized in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib plus docetaxel
Reporting group description:	
Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 milligram (mg)/square meter (m2) once every 3 weeks administered via intravenous infusion over 1 hour (h).	
Reporting group title	Placebo plus docetaxel
Reporting group description:	
Placebo soft gelatin capsule matching that of nintedanib 2 times daily plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).	

Reporting group values	Nintedanib plus docetaxel	Placebo plus docetaxel	Total
Number of subjects	655	659	1314
Age categorical Units: Subjects			
Age Continuous			
Randomised Set (RS)- Includes all randomised patients, whether patients had received study treatment or not			
Units: years			
arithmetic mean	59.7	59.8	
standard deviation	± 9.7	± 9.0	-
Sex: Female, Male			
Randomised Set			
Units: Subjects			
Female	179	180	359
Male	476	479	955
Tumour histology			
Randomised Set			
Units: Subjects			
Adenocarcinoma	322	336	658
Squamous cell carcinoma	276	279	555
Other	57	44	101
Number of patients with adenocarcinoma and time since first line therapy in categories			
Randomised Set			
Units: Subjects			
<9 month	206	199	405
>=9 month	112	134	246
Missing	4	3	7
No tumour histology of adenocarcinoma	333	323	656

End points

End points reporting groups

Reporting group title	Nintedanib plus docetaxel
Reporting group description:	
Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 milligram (mg)/square meter (m2) once every 3 weeks administered via intravenous infusion over 1 hour (h).	
Reporting group title	Placebo plus docetaxel
Reporting group description:	
Placebo soft gelatin capsule matching that of nintedanib 2 times daily plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).	
Subject analysis set title	Nitedanib 200 mg bid plus docetaxel
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).	
Subject analysis set title	Nintedanib 150 bid mg plus docetaxel
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Nintedanib 150 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).	

Primary: Progression Free Survival (PFS) as assessed by central independent review

End point title	Progression Free Survival (PFS) as assessed by central independent review
End point description:	
Progression Free Survival (PFS) as assessed by central independent review according to the modified Response Evaluation Criteria In Solid Tumors Criteria (RECIST) (version 1.0) criteria. Progression free survival (PFS) is defined as the duration of time from date of randomisation to date of progression or death (whatever occurs earlier). Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.	
End point type	Primary
End point timeframe:	
From randomisation until cut-off date 2 November 2010 (when 713 PFS events were observed)	

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	565[1]	569[2]		
Units: months				
median (inter-quartile range (Q1-Q3))	3.4 (1.5 to 5.7)	2.7 (1.4 to 4.6)		

Notes:

[1] - Randomised Set

[2] - Randomised Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1134

Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0019 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.92

Notes:

[3] - HR below 1 favors nintedanib

[4] - HR, CI and p-value obtained from the proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Secondary: Overall Survival (Key secondary endpoint)

End point title	Overall Survival (Key secondary endpoint)

End point description:

Overall Survival (OS) defined as the duration from randomisation to death (irrespective of the reason of death). Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. A fixed-sequence-testing was implemented for key secondary endpoint if both the primary and the follow-up analysis showed a treatment benefit (P<0.05) of nintedanib over placebo. In this case, the OS would be tested using hierarchical testing of statistical hypotheses in (1) patients with adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each hypothesis could be only tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013 (approximately 48 months or 1151 deaths among all patients)

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[5]	659[6]		
Units: months				
median (inter-quartile range (Q1-Q3))				
Adenocarcinoma and <9 months|	10.9 (5.1 to 21.9)	7.9 (4.5 to 14.5)		
Adenocarcinoma|	12.6 (5.5 to 24.2)	10.3 (5.5 to 19.9)		
All patients|	10.1 (5.0 to 19.4)	9.1 (4.8 to 17.2)		

Notes:

[5] - Randomised Set

[6] - Randomised Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hierarchical testing was tested in a fixed sequence of statistical hypotheses in (1) patients with

adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each hypothesis could be only tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been rejected. Overall survival for patients with adenocarcinoma and <9 months since start of first line therapy.

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0073 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.92

Notes:

[7] - The overall alpha level followed a Lan-DeMets spending function with O'Brien-Fleming shape parameter to preserve an overall 2-sided alpha level of 0.05. HR below 1 favors nintedanib

[8] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs 1 - one pat. had 2), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hierarchical testing was tested in a fixed sequence of statistical hypotheses in (1) patients with adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each hypothesis could be only tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been rejected. Overall survival for patients with adenocarcinoma.

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0359 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.99

Notes:

[9] - The overall alpha level followed a Lan-DeMets spending function with O'Brien-Fleming shape parameter to preserve an overall 2-sided alpha level of 0.05. HR below 1 favors nintedanib

[10] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs 1 - one pat. had 2), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Hierarchical testing was tested in a fixed sequence of statistical hypotheses in (1) patients with adenocarcinoma and <9 months since start of first-line therapy, (2) patients with adenocarcinoma, and (3) all patients. Each hypothesis could be only tested at the pre-specified alpha level if the previous null hypothesis in the testing sequence had been rejected. Overall survival for all patients.

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel

Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.272 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.05

Notes:

[11] - The overall alpha level followed a Lan-DeMets spending function with O'Brien-Fleming shape parameter to preserve an overall 2-sided alpha level of 0.05. HR below 1 favors nintedanib

[12] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs 1 - one pat. had 2), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Secondary: Follow-up analysis of Progression Free Survival (PFS) as Assessed by Central Independent Review

End point title	Follow-up analysis of Progression Free Survival (PFS) as Assessed by Central Independent Review

End point description:

Follow-up analysis was conducted at the time of overall survival analysis. Progression Free Survival (PFS) as assessed by central independent review according to the modified RECIST (version 1.0) criteria. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[13]	659[14]		
Units: months				
median (inter-quartile range (Q1-Q3))	3.5 (1.5 to 5.7)	2.7 (1.4 to 5.5)		

Notes:

[13] - Randomised Set

[14] - Randomised Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.007 [16]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	0.96

Notes:

[15] - HR below 1 favors nintedanib

[16] - HR, CI and p-value obtained from the proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Secondary: Follow-up analysis of Progression Free Survival (PFS) as Assessed by investigator

End point title	Follow-up analysis of Progression Free Survival (PFS) as Assessed by investigator

End point description:

Follow-up analysis was conducted at the time of overall survival analysis. Progression Free Survival (PFS) as assessed by investigator according to the modified RECIST (version 1.0) criteria. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[17]	659[18]		
Units: months				
median (inter-quartile range (Q1-Q3))	4.2 (2.1 to 7.1)	3.0 (1.4 to 5.7)		

Notes:

[17] - Randomised Set

[18] - Randomised Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0012 [20]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	0.93

Notes:

[19] - HR below 1 favors nintedanib

[20] - HR, CI and p-value obtained from the proportional hazards model stratified by baseline ECOG PS (0 vs 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Secondary: Objective Tumour Response

End point title	Objective Tumour Response

End point description:

Confirmed objective response is defined as confirmed Complete Response (CR) and Partial Response (PR) and evaluated according to the modified RECIST criteria version 1.0. As per RECIST v1.0, Complete Response (CR), disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions. This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[21]	659[22]		
Units: % of participants				
number (not applicable)				
central independent reviewer|	4.4	3.3		
investigator assessment|	10.4	7.6		

Notes:

[21] - Randomised Set

[22] - Randomised Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on the central independent review

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.3067 [24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.39

Notes:

[23] - An odds ratio >1 indicates a benefit to nintedanib

[24] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1)

	Statistical Analysis 2

Statistical analysis title	

Statistical analysis description:

Analysis based on the investigator's assessment

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.0761 [26]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	2.08

Notes:

[25] - An odds ratio >1 indicates a benefit to nintedanib

[26] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1)

Secondary: Duration of confirmed objective tumour response

End point title	Duration of confirmed objective tumour response

End point description:

The duration of objective response is the time from first documented (CR) or (PR) to the time of progression or death and evaluated according to the modified RECIST criteria version 1.0. As per RECIST v1.0, Complete Response (CR), disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[27]	659[28]		
Units: months				
median (inter-quartile range (Q1-Q3))				
central independent reviewer|	4.3 (3.0 to 5.7)	4.3 (2.8 to 8.5)		
investigator assessment|	5.7 (4.1 to 10.0)	5.5 (3.9 to 9.6)		

Notes:

[27] - Randomised Set

[28] - Randomised Set

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Confirmed Objective Tumour Response

End point title	Time to Confirmed Objective Tumour Response

End point description:

Time to confirmed objective response is defined as time from randomisation to the date of first documented (CR) or (PR) and evaluated according to the modified RECIST criteria version 1.0. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[29]	659[30]		
Units: months				
median (inter-quartile range (Q1-Q3))				
central independent reviewer|	1.5 (1.4 to 3.0)	2.9 (1.4 to 5.6)		
investigator assessment|	2.6 (1.4 to 4.0)	2.7 (1.4 to 4.1)		

Notes:

[29] - Randomised Set

[30] - Randomised Set

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control

End point title	Disease Control

End point description:

Disease control was defined as a best overall response of Complete Response (CR), Partial Response (PR), or Stable Disease (SD) and evaluated according to the modified RECIST criteria version 1.0. As per RECIST v1.0 for target lesions : Complete Response (CR), disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; progression, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression. This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[31]	659[32]		
Units: % of participants				
number (not applicable)				
central independent reviewer|	54.0	41.3		

investigator assessment|	63.4	51.4		

Notes:

[31] - Randomised Set

[32] - Randomised Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on the central independent review

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	< 0.0001 [34]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.35
upper limit	2.09

Notes:

[33] - An odds ratio >1 indicates a benefit to nintedanib

[34] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1)

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis based on investigator's assessment

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [35]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.31
upper limit	2.05

Notes:

[35] - Odds ratio and p-value are obtained from logistic regression model adjusted for baseline ECOG PS (0 vs 1)

Secondary: Duration of Disease Control

End point title	Duration of Disease Control

End point description:

The duration of disease control was defined as the time from randomisation to the date of disease progression or death (which ever occurs first) for patients with disease control. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve. This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[36]	659[37]		
Units: months				
median (inter-quartile range (Q1-Q3))				
central independent reviewer|	5.6 (4.1 to 7.1)	5.6 (4.0 to 8.2)		
investigator assessment|	5.7 (4.2 to 8.4)	5.6 (4.1 to 8.5)		

Notes:

[36] - Randomised Set

[37] - Randomised Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in tumour size

End point title	Change from baseline in tumour size

End point description:

Percentage change from baseline in tumour size is defined as decrease in the sum of the longest diameter of the target lesion. Presented means are in fact adjusted best means percentage changes generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no) This endpoint was analysed based on the central independent reviewer as well as the investigator.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[38]	659[39]		
Units: percentage of change in tumor size in mm				
arithmetic mean (confidence interval 95%)				
central independent reviewer|	-4.87 (-6.62 to -3.12)	0.58 (-1.19 to 2.35)		
investigator assessment|	-10.34 (-12.58 to -8.11)	-2.14 (-4.39 to 0.10)		

Notes:

[38] - Randomised Set

[39] - Randomised Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis based on the central independent review

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [40]
Method	ANOVA

Notes:

[40] - P-value generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis based on the investigator's assessment

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [41]
Method	ANOVA

Notes:

[41] - P-value generated from ANOVA model adjusted for baseline ECOG PS (0 vs. 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Secondary: Clinical improvement

End point title	Clinical improvement

End point description:

Clinical improvement was defined as the time from randomisation to deterioration in body weight and/or Eastern Cooperative Oncology group performance score (ECOG PS) whichever occurred first. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve.

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[42]	659[43]		
Units: months				
median (inter-quartile range (Q1-Q3))	5.9 (2.1 to 22.7)	5.2 (2.1 to 19.2)		

Notes:

[42] - Randomised set

[43] - Randomised set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.7282 [45]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.21

Notes:

[44] - HR below 1 favors nintedanib

[45] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs 1 - one pat.had 2), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Secondary: Quality of life (QoL)

End point title	Quality of life (QoL)

End point description:

QoL was measured by standardised questionnaires (EQ-5D, EORTC QLQ-C30, EORTC QLQ-LC13). The EORTC QLQ-C30 comprises of 30 questions, using both multi-item scales and single-item measures. EORTC LC-13 comprises of 13 questions incorporating 1 multi-item scale and a series of single items. The following were the main points of interest: Time to deterioration of cough (QLQ-LC13 question 1), Time to deterioration of dyspnoea (QLQ-LC13, composite of questions 3 to 5), Time to deterioration of pain (QLQ- C30, composite of questions 9 and 19). Time to deterioration of cough, dyspnoea and pain was defined as the time to a 10-point increase from the baseline score. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve

End point type	Secondary

End point timeframe:

From randomisation until cut-off date 15 February 2013

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[46]	659[47]		
Units: months				
median (inter-quartile range (Q1-Q3))				
Time to deterioration of cough|	4.3 (1.6 to 11.8)	3.5 (1.5 to 12.6)		
Time to deterioration of dyspnoea|	2.0 (0.8 to 4.2)	2.1 (0.8 to 4.5)		
Time to deterioration of pain|	2.8 (1.1 to 6.5)	2.6 (0.8 to 5.8)		

Notes:

[46] - Randomised set

[47] - Randomised set

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis evaluating the time to deterioration of cough	
Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.1858 [49]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.05

Notes:

[48] - HR below 1 favors nintedanib

[49] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >=1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Analysis evaluating the time to deterioration of dyspnoea	
Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.5203 [51]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.2

Notes:

[50] - HR below 1 favors nintedanib

[51] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >=1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis evaluating the time to deterioration of pain

Comparison groups	Nintedanib plus docetaxel v Placebo plus docetaxel
Number of subjects included in analysis	1314
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.4373 [53]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.09

Notes:

[52] - HR below 1 favors nintedanib

[53] - HR, CI and p-value obtained from the prop. hazards model stratified by baseline ECOG PS (0 vs >= 1), tumour histology (squamous vs non-squamous), brain metastases at baseline (yes vs no) and prior treatment with bevacizumab (yes vs no)

Secondary: Dose normalised predose plasma concentration at steady state (Cpre,ss,norm) of nintedanib and of its metabolites BIBF 1202 and BIBF 1202

End point title	Dose normalised predose plasma concentration at steady state (Cpre,ss,norm) of nintedanib and of its metabolites BIBF 1202 and BIBF 1202 glucuronide

End point description:

Geometric mean of dose normalised predose plasma concentration (Cpre,ss,norm) of nintedanib and of its metabolites BIBF 1202 and BIBF 1202 glucuronide evaluated at steady state based on course 2 and 3. If only one value was available and valid, then this value was used for calculation of Cpre,ss,norm.

End point type	Secondary

End point timeframe:

Before the administration of nintedanib or placebo and between a window of 30 mins to an hour after administration of trial drug during Course 2 and between 1 and 3 hours after administration of trial drug during Course 3

End point values	Nitedanib 200 mg bid plus docetaxel	Nintedanib 150 bid mg plus docetaxel		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	38		
Units: ng/mL/mg				
geometric mean (geometric coefficient of variation)				
nintedanib|	0.0707 (± 77.7)	0.106 (± 52.6)		
metabolite BIBF 1202|	0.0907 (± 127)	0.190 (± 152)		

metabolite BIBF 1202 glucuronide|	1.04 (± 153)	1.94 (± 135)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and intensity of adverse events

End point title	Incidence and intensity of adverse events

End point description:

Incidence and intensity of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The worst CTCAE grade per patient is reported and MedDRA version 15.1 used. Serious signs and symptoms of progressive disease were reported as an adverse event in analysis of this endpoint. Treated set- all randomised patients who were documented to have taken at least 1 dose of study medication . Patients were allocated to the treatment groups according to the treatment actually received.

End point type	Secondary

End point timeframe:

From the first drug administration until 28 days after the last drug administration, up to 42 months

End point values	Nintedanib plus docetaxel	Placebo plus docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	655[54]	659[55]		
Units: % of participants				
number (not applicable)				
Grade 1	5.7	8.2		
Grade 2	16.6	20.5		
Grade 3	21.2	21.2		
Grade 4	33.7	31.3		
Grade 5	16.4	11.8		

Notes:

[54] - Treated set

[55] - Treated set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration, up to 42 months.

Adverse event reporting additional description:

Number of participants at risk corresponds to all randomised patients who were documented to have taken at least 1 dose of study medication . Patients were allocated to the treatment groups according to the treatment actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Placebo plus docetaxel

Reporting group description:

Placebo soft gelatin capsule matching that of nintedanib 2 times daily plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).

Reporting group title	Nintedanib plus docetaxel

Reporting group description:

Nintedanib 200 mg twice daily administered orally in the form of a soft gelatin capsule plus docetaxel 75 mg/m2 once every 3 weeks administered via intravenous infusion over 1 hour (h).

Serious adverse events	Placebo plus docetaxel	Nintedanib plus docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	206 / 655 (31.45%)	224 / 652 (34.36%)	
number of deaths (all causes)	562	565	
number of deaths resulting from adverse events	77	107	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 655 (0.15%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	

Hypotension			
subjects affected / exposed	1 / 655 (0.15%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery thrombosis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombosis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Venous thrombosis limb			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer metastatic			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Malignant neoplasm progression			
subjects affected / exposed	17 / 655 (2.60%)	25 / 652 (3.83%)	
occurrences causally related to treatment / all	0 / 17	1 / 25	
deaths causally related to treatment / all	0 / 15	1 / 25	
Metastases to central nervous system			
subjects affected / exposed	2 / 655 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to chest wall			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to kidney			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 655 (0.00%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Metastases to skin			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			

subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 655 (0.31%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	3 / 655 (0.46%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 655 (0.61%)	7 / 652 (1.07%)	
occurrences causally related to treatment / all	0 / 4	1 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Chest discomfort			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	8 / 655 (1.22%)	7 / 652 (1.07%)	
occurrences causally related to treatment / all	1 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 2	
Condition aggravated			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	1 / 655 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Device occlusion			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 655 (0.15%)	7 / 652 (1.07%)	
occurrences causally related to treatment / all	1 / 1	5 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
Feeling abnormal			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	8 / 655 (1.22%)	11 / 652 (1.69%)	
occurrences causally related to treatment / all	2 / 8	4 / 12	
deaths causally related to treatment / all	0 / 6	0 / 8	
Malaise			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 655 (0.15%)	2 / 652 (0.31%)	

occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Oedema peripheral			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organ failure			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	9 / 655 (1.37%)	7 / 652 (1.07%)	
occurrences causally related to treatment / all	3 / 11	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depression			
subjects affected / exposed	0 / 655 (0.00%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	3 / 655 (0.46%)	0 / 652 (0.00%)	
occurrences causally related to	0 / 3	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 1	0 / 0	
Mental disorder due to a general medical condition			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Panic attack			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	2 / 655 (0.31%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	3 / 655 (0.46%)	6 / 652 (0.92%)	
occurrences causally related to treatment / all	3 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	2 / 655 (0.31%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 655 (0.31%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to	0 / 0	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 655 (0.46%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	0 / 655 (0.00%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	

deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 655 (0.15%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Alveolitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 655 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchial haemorrhage			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial secretion retention			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchostenosis			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	2 / 655 (0.31%)	3 / 652 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dysphonia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	30 / 655 (4.58%)	24 / 652 (3.68%)	
occurrences causally related to treatment / all	2 / 33	1 / 25	
deaths causally related to treatment / all	1 / 12	0 / 15	
Hypoxia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	7 / 655 (1.07%)	6 / 652 (0.92%)	
occurrences causally related to treatment / all	1 / 7	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 4	

Interstitial lung disease			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oropharyngeal pain			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	8 / 655 (1.22%)	8 / 652 (1.23%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pleuritic pain			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
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 / 655 (0.00%)	1 / 652 (0.15%)	
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 / 655 (0.15%)	3 / 652 (0.46%)	

occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 655 (0.92%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	2 / 6	2 / 4	
deaths causally related to treatment / all	1 / 3	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	3 / 655 (0.46%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	1 / 3	1 / 5	
deaths causally related to treatment / all	1 / 3	0 / 3	
Respiratory depression			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 655 (0.31%)	8 / 652 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 8	
Stridor			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal stenosis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 655 (0.92%)	2 / 652 (0.31%)	
occurrences causally related to	3 / 6	1 / 3	

treatment / all			
deaths causally related to treatment / all	1 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	19 / 655 (2.90%)	30 / 652 (4.60%)	
occurrences causally related to treatment / all	12 / 20	27 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukopenia			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	21 / 655 (3.21%)	21 / 652 (3.22%)	
occurrences causally related to treatment / all	20 / 24	18 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	

occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Convulsion			
subjects affected / exposed	0 / 655 (0.00%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diplegia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	

deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiduritis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Ischaemic stroke			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Lethargy			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Monoparesis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restless legs syndrome			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 655 (0.61%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	2 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	13 / 655 (1.98%)	16 / 652 (2.45%)	
occurrences causally related to treatment / all	11 / 13	13 / 16	
deaths causally related to treatment / all	0 / 0	1 / 1	
Diverticulum intestinal			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	

occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Nausea			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 655 (0.46%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	7 / 655 (1.07%)	8 / 652 (1.23%)	
occurrences causally related to treatment / all	3 / 7	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder perforation			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystocholangitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 655 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
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	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	1 / 655 (0.15%)	5 / 652 (0.77%)	
occurrences causally related to treatment / all	1 / 1	4 / 6	

deaths causally related to treatment / all	0 / 0	1 / 1	
Hypercalcaemia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 655 (0.00%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess rupture			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 655 (0.61%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Empyema			
subjects affected / exposed	1 / 655 (0.15%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 655 (0.31%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 655 (0.15%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngitis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 655 (0.46%)	4 / 652 (0.61%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lung abscess			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infection			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenic sepsis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Opportunistic infection			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	26 / 655 (3.97%)	17 / 652 (2.61%)	
occurrences causally related to treatment / all	8 / 28	2 / 17	

deaths causally related to treatment / all	2 / 8	0 / 3	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 655 (0.46%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 655 (0.46%)	7 / 652 (1.07%)	
occurrences causally related to treatment / all	0 / 3	4 / 7	
deaths causally related to treatment / all	0 / 1	3 / 5	
Septic shock			
subjects affected / exposed	0 / 655 (0.00%)	2 / 652 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Streptococcal infection			
subjects affected / exposed	1 / 655 (0.15%)	0 / 652 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 655 (0.00%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 655 (0.46%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	2 / 655 (0.31%)	1 / 652 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo plus docetaxel	Nintedanib plus docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	547 / 655 (83.51%)	569 / 652 (87.27%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	55 / 655 (8.40%)	186 / 652 (28.53%)	
occurrences (all)	76	320	
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 655 (1.37%)	38 / 652 (5.83%)	
occurrences (all)	9	43	
Aspartate aminotransferase increased			
subjects affected / exposed	43 / 655 (6.56%)	146 / 652 (22.39%)	
occurrences (all)	53	242	
Haemoglobin decreased			
subjects affected / exposed	79 / 655 (12.06%)	71 / 652 (10.89%)	
occurrences (all)	103	99	
Neutrophil count decreased			
subjects affected / exposed	234 / 655 (35.73%)	237 / 652 (36.35%)	
occurrences (all)	574	682	
White blood cell count decreased			
subjects affected / exposed	160 / 655 (24.43%)	158 / 652 (24.23%)	
occurrences (all)	402	476	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	108 / 655 (16.49%)	97 / 652 (14.88%)	
occurrences (all)	126	110	
Dyspnoea			
subjects affected / exposed	83 / 655 (12.67%)	102 / 652 (15.64%)	

occurrences (all)	98	111	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	43 / 655 (6.56%)	33 / 652 (5.06%)	
occurrences (all)	49	40	
Neutropenia			
subjects affected / exposed	78 / 655 (11.91%)	77 / 652 (11.81%)	
occurrences (all)	193	142	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	34 / 655 (5.19%)	31 / 652 (4.75%)	
occurrences (all)	43	35	
Dizziness			
subjects affected / exposed	35 / 655 (5.34%)	31 / 652 (4.75%)	
occurrences (all)	38	34	
Peripheral sensory neuropathy			
subjects affected / exposed	47 / 655 (7.18%)	40 / 652 (6.13%)	
occurrences (all)	51	45	
Headache			
subjects affected / exposed	42 / 655 (6.41%)	39 / 652 (5.98%)	
occurrences (all)	44	41	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	61 / 655 (9.31%)	52 / 652 (7.98%)	
occurrences (all)	77	58	
Chest pain			
subjects affected / exposed	57 / 655 (8.70%)	49 / 652 (7.52%)	
occurrences (all)	71	52	
Fatigue			
subjects affected / exposed	175 / 655 (26.72%)	192 / 652 (29.45%)	
occurrences (all)	231	252	
Oedema peripheral			
subjects affected / exposed	42 / 655 (6.41%)	35 / 652 (5.37%)	
occurrences (all)	52	38	
Pyrexia			

subjects affected / exposed	92 / 655 (14.05%)	77 / 652 (11.81%)	
occurrences (all)	129	108	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	38 / 655 (5.80%)	31 / 652 (4.75%)	
occurrences (all)	43	35	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	37 / 655 (5.65%)	35 / 652 (5.37%)	
occurrences (all)	45	41	
Constipation			
subjects affected / exposed	76 / 655 (11.60%)	35 / 652 (5.37%)	
occurrences (all)	97	43	
Diarrhoea			
subjects affected / exposed	134 / 655 (20.46%)	267 / 652 (40.95%)	
occurrences (all)	196	518	
Stomatitis			
subjects affected / exposed	56 / 655 (8.55%)	62 / 652 (9.51%)	
occurrences (all)	67	78	
Nausea			
subjects affected / exposed	118 / 655 (18.02%)	158 / 652 (24.23%)	
occurrences (all)	172	231	
Vomiting			
subjects affected / exposed	56 / 655 (8.55%)	102 / 652 (15.64%)	
occurrences (all)	96	152	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	119 / 655 (18.17%)	107 / 652 (16.41%)	
occurrences (all)	121	107	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	46 / 655 (7.02%)	40 / 652 (6.13%)	
occurrences (all)	52	55	
Back pain			
subjects affected / exposed	44 / 655 (6.72%)	27 / 652 (4.14%)	
occurrences (all)	53	34	

Myalgia			
subjects affected / exposed	45 / 655 (6.87%)	40 / 652 (6.13%)	
occurrences (all)	64	53	
Pain in extremity			
subjects affected / exposed	41 / 655 (6.26%)	31 / 652 (4.75%)	
occurrences (all)	45	39	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	102 / 655 (15.57%)	145 / 652 (22.24%)	
occurrences (all)	115	173	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2009	With Protocol Amendment 1, Revise typing errors that were detected in the original protocol. Addition of a statement with regard to the tasks and members of the Data Monitoring Committee (DMC), addition of a statement concerning docetaxel hypersensitivity, addition of an additional safety laboratory test in case of bilirubin increase, addition of food intake on the days of and the days preceding pharmacokinetic blood sampling, clarification of one exclusion criterion, allow extension of screening period in exceptional situations
12 February 2014	Prior to the amendment, patients who had stopped active treatment were to be followed-up until death or lost to follow-up. Since the analysis of the key secondary end point OS was complete, the follow-up period for patients who had stopped active treatment was reduced to 28 days which was the reporting period for AEs (after last administration of trial medication). With Protocol Amendment 2, the end of the trial was redefined. The clinical trial was considered completed as soon as the last patient had completed the first follow-up visit which was recommended to take place at least 28 days after end of active treatment (EOT). It was clarified that data collected after the cut-off date of the final OS analysis will be reported in a revision of the CTR.
16 April 2015	The European Commission granted marketing authorisation for nintedanib (Vargatef®) in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy on 21 November 2014. With Protocol Amendment 3, all patients still on treatment were unblinded; patients in the placebo arm were given the opportunity to be treated with BIBF1120 and patients in the active arm were allowed to continue to be treated with BIBF1120. Since the trial was complete and no further cumulative data analyses were planned, efficacy assessment were to be done according to standard practice but were no longer collected in the CRF. Safety assessments were to be done as clinically indicated. Adverse events (AEs) were still reported in the CRF. Reporting requirements for SAEs remained the same. All sections f the clinical trial protocol affected by unblinding of the remaining patients, the switch from placebo to BIBF 1120, and the new procedures regarding data collection were revised. It was clarified that only clinically significant physical examination findings were to be reported in the CRF as an AE. New packaging of BIBF 1120 and a new distribution process were described. It was clarified that placebo was no longer provided to patients. The end of the trial was redefined. The clinical trial was considered completed as soon as the last patient was transferred to another programme or had completed the first follow-up visit which was recommended to take place 28 days after end of active treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported