



## Clinical trial results:

### Phase III study comparing the efficacy of paclitaxel-bevacizumab with docetaxel in 2nd or 3rd line of treatment of non squamous Non Small Cell Lung Cancer

#### Summary

EudraCT number	2012-004524-38
Trial protocol	FR
Global end of trial date	12 April 2017

#### Results information

Result version number	v1
This version publication date	08 April 2021
First version publication date	08 April 2021

#### Trial information

##### Trial identification

Sponsor protocol code	IFCT-1103 Ultimate
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01763671
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 rue de la Grange-Batelière, PARIS, France, 75009
Public contact	Responsable communication, IFCT, 33 156811046, contact@ifct.fr
Scientific contact	Responsable communication, IFCT, 33 156811046, contact@ifct.fr

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	29 June 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 April 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Progression free survival

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2013
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	France: 166
Worldwide total number of subjects	166
EEA total number of subjects	166

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)	117
From 65 to 84 years	49
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 166 randomised patients [Paclitaxel-Bevacizumab group: 111 (67%), Docetaxel group: 55 (33%)] was included between May 31, 2013 and August 13, 2014.

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

Number of subjects started	166
Number of subjects completed	166

### Period 1

Period 1 title	Sequence 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Arm A - Docetaxel (DOC)
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 75 mg/m<sup>2</sup> every 21 days

<b>Arm title</b>	Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

paclitaxel 90 mg/m<sup>2</sup> D1, D8, D15 every 28 days

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

Dosage and administration details:

bevacizumab 10 mg/kg D1, D15 every 28 days

Number of subjects in period 1	Arm A - Docetaxel (DOC)	Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)
Started	55	111
Completed	55	109
Not completed	0	2
Physician decision	-	1
Disease progression	-	1

## Period 2

Period 2 title	Sequence 2 (Cross-Over)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Arm B1 - Paclitaxel plus bevacizumab (cross-over)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

paclitaxel 90 mg/m<sup>2</sup> D1, D8, D15 every 28 days

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

Dosage and administration details:

bevacizumab 10 mg/kg D1, D15 every 28 days

<b>Arm title</b>	Arm A1 - Docetaxel (cross-over)
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

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Dosage and administration details:  
Docetaxel 75 mg/m<sup>2</sup> every 21 days

<b>Number of subjects in period 2<sup>[1]</sup></b>	Arm B1 - Paclitaxel plus bevacizumab (cross-over)	Arm A1 - Docetaxel (cross-over)
Started	21	9
Completed	21	9

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients were allowed to cross-over to the other arm following disease progression over the study. This cross-over was optional.

## Baseline characteristics

### Reporting groups

Reporting group title	Arm A - Docetaxel (DOC)
Reporting group description: -	
Reporting group title	Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)
Reporting group description: -	

Reporting group values	Arm A - Docetaxel (DOC)	Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)	Total
Number of subjects	55	111	166
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	60.74	59.57	-
standard deviation	± 9.44	± 9.38	-
Gender categorical			
Units: Subjects			
Female	13	78	91
Male	42	33	75
Smoking			
Units: Subjects			
No	9	9	18
Yes	46	102	148
PS			
Units: Subjects			
PS 0	20	47	67
PS 1	31	56	87
PS 2	4	8	12
Histology			
Units: Subjects			
Adenocarcinoma	51	100	151
Large cells/No	4	11	15
Previous exposure to bevacizumab			
Units: Subjects			
No	38	77	115
Yes	17	34	51

Number of previous lines Units: Subjects			
1 line	39	76	115
2 lines	14	34	48
3 lines	2	1	3
Time between the diagnostic of cancer and inclusion Units: Subjects			
< 9 months	20	52	72
> 9 months	35	59	94
Age class Units: Subjects			
< 70 years old	45	101	146
> 70 years old	10	10	20
Weight loss Units: Subjects			
< 0 kg	12	20	32
0 - 5 kg	42	85	127
5 - 10 kg	1	4	5
missing	0	2	2
EGFR Units: Subjects			
Activating mutation	2	4	6
Resistance mutation	1	0	1
Other mutation	0	1	1
Wild-type	44	87	131
Inderminate	5	9	14
Not done	3	10	13
Weight Units: kilogram(s)			
arithmetic mean	69.18	69.05	
standard deviation	± 12.47	± 13.72	-
Number of pack-year Units: pack-years			
arithmetic mean	44.11	37.38	
standard deviation	± 23.54	± 21.40	-

## End points

### End points reporting groups

Reporting group title	Arm A - Docetaxel (DOC)
Reporting group description: -	
Reporting group title	Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)
Reporting group description: -	
Reporting group title	Arm B1 - Paclitaxel plus bevacizumab (cross-over)
Reporting group description: -	
Reporting group title	Arm A1 - Docetaxel (cross-over)
Reporting group description: -	

### Primary: Progression free survival

End point title	Progression free survival
End point description:	
End point type	Primary
End point timeframe:	
Time between randomisation and disease progression (as assessed by the investigator using RECIST 1.1) or death from any cause, whatever came first.	

End point values	Arm A - Docetaxel (DOC)	Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	109		
Units: months				
number (confidence interval 95%)	3.9 (2.69 to 5.26)	5.4 (4.63 to 7.13)		

### Statistical analyses

Statistical analysis title	Progression Free Survival
Statistical analysis description:	
Time between randomisation and disease progression (as assessed by the investigator using RECIST 1.1) or death from any cause, whatever came first.	
Comparison groups	Arm A - Docetaxel (DOC) v Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.86

### Secondary: Response Rate

End point title	Response Rate
End point description:	
End point type	Secondary
End point timeframe:	
At 8 weeks	

End point values	Arm A - Docetaxel (DOC)	Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	109		
Units: Percentage				
Not Done / Not Evaluable	4	10		
Progression	19	21		
Objective response	3	25		
Stable	29	55		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

End point title	Overall survival
End point description:	
End point type	Secondary
End point timeframe:	
Overall survival is defined as time between date of inclusion and all-cause death	

<b>End point values</b>	Arm A - Docetaxel (DOC)	Arm B - Paclitaxel plus bevacizumab (wPAC-BEV)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	109		
Units: months				
number (confidence interval 95%)	11.4 (7.85 to 13.14)	9.9 (8.11 to 12.2)		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse events have to be reported from inclusion to 30 day following the end of administration of study treatments.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18

### Reporting groups

Reporting group title	Safety population - Arm A
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Reporting group description:

The safety population - Arm A will be defined as all patients who received at least one dose of docetaxel.

Reporting group title	Safety population - Arm B
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Reporting group description:

The safety population - Arm B will be defined as all patients who received at least one dose of paclitaxel and bevacizumab.

Reporting group title	Safety population - Arm A1
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Reporting group description:

The safety population - Arm A1 will be defined as all patients who received at least one dose of docetaxel during cross-over.

Reporting group title	Safety population - Arm B1
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Reporting group description:

The safety population - Arm B1 will be defined as all patients who received at least one dose of paclitaxel-bevacizumab during cross-over.

<b>Serious adverse events</b>	Safety population - Arm A	Safety population - Arm B	Safety population - Arm A1
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 55 (16.36%)	15 / 109 (13.76%)	1 / 9 (11.11%)
number of deaths (all causes)	32	94	9
number of deaths resulting from adverse events	3	2	0
Vascular disorders			
Esophagitis hemorrhagic			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 55 (1.82%)	2 / 109 (1.83%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reduced general condition			
subjects affected / exposed	1 / 55 (1.82%)	2 / 109 (1.83%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug allergy			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dyspnea			
subjects affected / exposed	0 / 55 (0.00%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Esophagobronchial fistula			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hypoxia			
subjects affected / exposed	1 / 55 (1.82%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Interstitial pneumonitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumopathy			
subjects affected / exposed	2 / 55 (3.64%)	3 / 109 (2.75%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Pulmonary embolism</b>			
subjects affected / exposed	0 / 55 (0.00%)	2 / 109 (1.83%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Respiratory failure</b>			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Investigations</b>			
<b>Neutrophil count decreased</b>			
subjects affected / exposed	2 / 55 (3.64%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Injury, poisoning and procedural complications</b>			
<b>Fall</b>			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac disorders</b>			
<b>Arrhythmia</b>			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Atrial fibrillation</b>			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Nervous system disorders</b>			
<b>Confusion</b>			

subjects affected / exposed	0 / 55 (0.00%)	0 / 109 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Neuropathy</b>			
subjects affected / exposed	0 / 55 (0.00%)	2 / 109 (1.83%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Stroke</b>			
subjects affected / exposed	0 / 55 (0.00%)	2 / 109 (1.83%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
<b>Blood and lymphatic system disorders</b>			
<b>Agranulocytosis</b>			
subjects affected / exposed	0 / 55 (0.00%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Aplasia bone marrow</b>			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Febrile aplasia</b>			
subjects affected / exposed	1 / 55 (1.82%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Febrile neutropenia</b>			
subjects affected / exposed	2 / 55 (3.64%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Gastrointestinal disorders</b>			
<b>Vomiting</b>			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Skin and subcutaneous tissue disorders</b>			

Hand-and-foot syndrome			
subjects affected / exposed	1 / 55 (1.82%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 55 (1.82%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fracture NOS			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Catheter related infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection NOS			
subjects affected / exposed	1 / 55 (1.82%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Oral candida			
subjects affected / exposed	0 / 55 (0.00%)	0 / 109 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystosis			

subjects affected / exposed	1 / 55 (1.82%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Sepsis</b>			
subjects affected / exposed	1 / 55 (1.82%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Metabolism and nutrition disorders</b>			
<b>Dehydration</b>			
subjects affected / exposed	0 / 55 (0.00%)	0 / 109 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Safety population - Arm B1		
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	3 / 21 (14.29%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events	0		
<b>Vascular disorders</b>			
<b>Esophagitis hemorrhagic</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>General disorders and administration site conditions</b>			
<b>Fever</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Reduced general condition</b>			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Immune system disorders</b>			
<b>Drug allergy</b>			

subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Reproductive system and breast disorders</b>			
Dyspnea			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Respiratory, thoracic and mediastinal disorders</b>			
Esophagobronchial fistula			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial pneumonitis			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumopathy			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory failure			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Confusion			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuropathy			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stroke			

subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Blood and lymphatic system disorders</b>			
<b>Agranulocytosis</b>			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Aplasia bone marrow</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Febrile aplasia</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Febrile neutropenia</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Gastrointestinal disorders</b>			
<b>Vomiting</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Skin and subcutaneous tissue disorders</b>			
<b>Hand-and-foot syndrome</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders</b>			
<b>Renal failure</b>			

subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Musculoskeletal and connective tissue disorders</b>			
Fracture NOS			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Catheter related infection			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection NOS			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oral candida			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural infection			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumocystosis			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Safety population - Arm A	Safety population - Arm B	Safety population - Arm A1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 55 (98.18%)	109 / 109 (100.00%)	9 / 9 (100.00%)
Vascular disorders			
Epistaxis			
subjects affected / exposed	2 / 55 (3.64%)	47 / 109 (43.12%)	0 / 9 (0.00%)
occurrences (all)	5	81	0
Hypertension			
subjects affected / exposed	0 / 55 (0.00%)	24 / 109 (22.02%)	1 / 9 (11.11%)
occurrences (all)	0	33	1
Pulmonary embolism			
subjects affected / exposed	1 / 55 (1.82%)	8 / 109 (7.34%)	0 / 9 (0.00%)
occurrences (all)	1	15	0
Haemoptysis			
subjects affected / exposed	3 / 55 (5.45%)	6 / 109 (5.50%)	0 / 9 (0.00%)
occurrences (all)	5	7	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 55 (54.55%)	65 / 109 (59.63%)	2 / 9 (22.22%)
occurrences (all)	70	145	2
Oedema peripheral			
subjects affected / exposed	5 / 55 (9.09%)	16 / 109 (14.68%)	0 / 9 (0.00%)
occurrences (all)	8	20	0
Fatigue			
subjects affected / exposed	2 / 55 (3.64%)	5 / 109 (4.59%)	1 / 9 (11.11%)
occurrences (all)	3	7	1
General physical health deterioration			

subjects affected / exposed	9 / 55 (16.36%)	8 / 109 (7.34%)	3 / 9 (33.33%)
occurrences (all)	9	9	3
Oedema			
subjects affected / exposed	0 / 55 (0.00%)	1 / 109 (0.92%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Diarrhoea			
subjects affected / exposed	13 / 55 (23.64%)	26 / 109 (23.85%)	1 / 9 (11.11%)
occurrences (all)	23	38	1
Chest pain			
subjects affected / exposed	7 / 55 (12.73%)	10 / 109 (9.17%)	1 / 9 (11.11%)
occurrences (all)	13	13	1
Pyrexia			
subjects affected / exposed	6 / 55 (10.91%)	7 / 109 (6.42%)	1 / 9 (11.11%)
occurrences (all)	7	9	1
Face oedema			
subjects affected / exposed	3 / 55 (5.45%)	0 / 109 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 55 (1.82%)	13 / 109 (11.93%)	0 / 9 (0.00%)
occurrences (all)	1	22	0
Dyspnoea			
subjects affected / exposed	16 / 55 (29.09%)	25 / 109 (22.94%)	2 / 9 (22.22%)
occurrences (all)	27	42	2
Lung disorder			
subjects affected / exposed	2 / 55 (3.64%)	3 / 109 (2.75%)	1 / 9 (11.11%)
occurrences (all)	3	3	1
Cough			
subjects affected / exposed	17 / 55 (30.91%)	31 / 109 (28.44%)	2 / 9 (22.22%)
occurrences (all)	29	70	2
Dyspnoea exertional			
subjects affected / exposed	4 / 55 (7.27%)	5 / 109 (4.59%)	0 / 9 (0.00%)
occurrences (all)	7	8	0
Productive cough			

subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 5	5 / 109 (4.59%) 8	0 / 9 (0.00%) 0
Pneumothorax subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	3 / 109 (2.75%) 5	0 / 9 (0.00%) 0
Pulmonary congestion subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	0 / 109 (0.00%) 0	0 / 9 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	7 / 109 (6.42%) 8	0 / 9 (0.00%) 0
Investigations Weight decreased subjects affected / exposed occurrences (all)	9 / 55 (16.36%) 10	16 / 109 (14.68%) 18	2 / 9 (22.22%) 2
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	6 / 55 (10.91%) 15	13 / 109 (11.93%) 18	2 / 9 (22.22%) 2
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 3	6 / 109 (5.50%) 8	2 / 9 (22.22%) 2
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	8 / 109 (7.34%) 12	0 / 9 (0.00%) 0
Nervous system disorders Paraesthesia subjects affected / exposed occurrences (all)	10 / 55 (18.18%) 25	40 / 109 (36.70%) 72	3 / 9 (33.33%) 3
Neuropathy peripheral subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 10	22 / 109 (20.18%) 60	0 / 9 (0.00%) 0
Dysgeusia subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	8 / 109 (7.34%) 13	0 / 9 (0.00%) 0
Hypoaesthesia			

subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 6	0 / 109 (0.00%) 0	0 / 9 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	6 / 55 (10.91%) 6	14 / 109 (12.84%) 21	1 / 9 (11.11%) 1
Sciatica subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 5	3 / 109 (2.75%) 4	0 / 9 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	1 / 109 (0.92%) 1	2 / 9 (22.22%) 2
Monoparesis subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	0 / 109 (0.00%) 0	2 / 9 (22.22%) 2
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	40 / 55 (72.73%) 119	67 / 109 (61.47%) 144	6 / 9 (66.67%) 6
Neutropenia subjects affected / exposed occurrences (all)	31 / 55 (56.36%) 68	50 / 109 (45.87%) 110	4 / 9 (44.44%) 6
Thrombocytopenia subjects affected / exposed occurrences (all)	13 / 55 (23.64%) 19	13 / 109 (11.93%) 25	1 / 9 (11.11%) 1
Febrile neutropenia subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4	1 / 109 (0.92%) 1	0 / 9 (0.00%) 0
Febrile bone marrow aplasia subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	0 / 109 (0.00%) 0	1 / 9 (11.11%) 1
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	7 / 109 (6.42%) 10	0 / 9 (0.00%) 0
Eye disorders			

Lacrimation increased subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 6	1 / 109 (0.92%) 3	0 / 9 (0.00%) 0
<b>Gastrointestinal disorders</b>			
Nausea subjects affected / exposed occurrences (all)	13 / 55 (23.64%) 15	28 / 109 (25.69%) 43	1 / 9 (11.11%) 1
Stomatitis subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 5	21 / 109 (19.27%) 31	1 / 9 (11.11%) 1
Constipation subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4	28 / 109 (25.69%) 36	1 / 9 (11.11%) 1
Vomiting subjects affected / exposed occurrences (all)	7 / 55 (12.73%) 7	20 / 109 (18.35%) 27	0 / 9 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 8	6 / 109 (5.50%) 8	0 / 9 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	9 / 109 (8.26%) 12	2 / 9 (22.22%) 2
Subileus subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	0 / 109 (0.00%) 0	1 / 9 (11.11%) 1
<b>Skin and subcutaneous tissue disorders</b>			
Alopecia subjects affected / exposed occurrences (all)	19 / 55 (34.55%) 36	32 / 109 (29.36%) 57	1 / 9 (11.11%) 1
Nail disorder subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 2	5 / 109 (4.59%) 12	0 / 9 (0.00%) 0
Onycholysis subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	4 / 109 (3.67%) 8	0 / 9 (0.00%) 0
Dry skin			

subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 6	6 / 109 (5.50%) 13	0 / 9 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 6	4 / 109 (3.67%) 7	0 / 9 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	4 / 109 (3.67%) 6	0 / 9 (0.00%) 0
Rash erythematous subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	0 / 109 (0.00%) 0	1 / 9 (11.11%) 1
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	23 / 109 (21.10%) 49	0 / 9 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	6 / 55 (10.91%) 10	19 / 109 (17.43%) 36	1 / 9 (11.11%) 1
Arthralgia subjects affected / exposed occurrences (all)	6 / 55 (10.91%) 14	15 / 109 (13.76%) 29	1 / 9 (11.11%) 1
Pain in extremity subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 6	7 / 109 (6.42%) 9	0 / 9 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 5	6 / 109 (5.50%) 6	0 / 9 (0.00%) 0
Bone pain subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	5 / 109 (4.59%) 5	1 / 9 (11.11%) 1
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 3	6 / 109 (5.50%) 8	0 / 9 (0.00%) 0
Neck pain			

subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	3 / 109 (2.75%) 4	1 / 9 (11.11%) 1
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 5	0 / 109 (0.00%) 0	0 / 9 (0.00%) 0
Amyotrophy subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	0 / 109 (0.00%) 0	1 / 9 (11.11%) 1
<b>Infections and infestations</b>			
Paronychia subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	4 / 109 (3.67%) 5	1 / 9 (11.11%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	4 / 109 (3.67%) 4	1 / 9 (11.11%) 1
Bronchitis subjects affected / exposed occurrences (all)	6 / 55 (10.91%) 6	10 / 109 (9.17%) 10	0 / 9 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	7 / 109 (6.42%) 15	0 / 9 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 3	6 / 109 (5.50%) 15	0 / 9 (0.00%) 0
Lung infection subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	6 / 109 (5.50%) 6	0 / 9 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	6 / 109 (5.50%) 7	0 / 9 (0.00%) 0
Tooth abscess subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	5 / 109 (4.59%) 6	0 / 9 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	2 / 109 (1.83%) 2	0 / 9 (0.00%) 0

Infection subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	2 / 109 (1.83%) 2	1 / 9 (11.11%) 1
Metabolism and nutrition disorders			
Myalgia subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 4	9 / 109 (8.26%) 20	0 / 9 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	13 / 55 (23.64%) 29	27 / 109 (24.77%) 41	4 / 9 (44.44%) 5
Hypercreatinaemia subjects affected / exposed occurrences (all)	11 / 55 (20.00%) 46	12 / 109 (11.01%) 33	1 / 9 (11.11%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 5	8 / 109 (7.34%) 16	0 / 9 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	9 / 109 (8.26%) 25	1 / 9 (11.11%) 2
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 3	7 / 109 (6.42%) 15	1 / 9 (11.11%) 2
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	3 / 109 (2.75%) 6	1 / 9 (11.11%) 1
Malnutrition subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	2 / 109 (1.83%) 2	1 / 9 (11.11%) 1

<b>Non-serious adverse events</b>	Safety population - Arm B1		
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 21 (95.24%)		
Vascular disorders			
Epistaxis subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 5		
Hypertension			

subjects affected / exposed	6 / 21 (28.57%)		
occurrences (all)	16		
<b>Pulmonary embolism</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
<b>Haemoptysis</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
<b>General disorders and administration site conditions</b>			
<b>Asthenia</b>			
subjects affected / exposed	9 / 21 (42.86%)		
occurrences (all)	28		
<b>Oedema peripheral</b>			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
<b>Fatigue</b>			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	4		
<b>General physical health deterioration</b>			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
<b>Oedema</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
<b>Diarrhoea</b>			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	4		
<b>Chest pain</b>			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	5		
<b>Pyrexia</b>			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	3		
<b>Face oedema</b>			

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			
Dysphonia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Dyspnoea subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 10		
Lung disorder subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Cough subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 7		
Dyspnoea exertional subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Productive cough subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 6		
Pneumothorax subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3		
Pulmonary congestion subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 4		
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 8		
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Nervous system disorders			
Paraesthesia subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 5		
Neuropathy peripheral subjects affected / exposed occurrences (all)	8 / 21 (38.10%) 14		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Sciatica subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 4		
Confusional state subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Monoparesis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed occurrences (all)	16 / 21 (76.19%) 30		
Neutropenia subjects affected / exposed occurrences (all)	7 / 21 (33.33%) 17		
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 3		
Febrile neutropenia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Febrile bone marrow aplasia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 5		
Stomatitis subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 5		
Constipation subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 5		
Vomiting subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Abdominal pain			

<p>subjects affected / exposed occurrences (all)</p> <p>Abdominal pain upper subjects affected / exposed occurrences (all)</p> <p>Subileus subjects affected / exposed occurrences (all)</p>	<p>2 / 21 (9.52%) 4</p> <p>0 / 21 (0.00%) 0</p> <p>0 / 21 (0.00%) 0</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Alopecia subjects affected / exposed occurrences (all)</p> <p>Nail disorder subjects affected / exposed occurrences (all)</p> <p>Onycholysis subjects affected / exposed occurrences (all)</p> <p>Dry skin subjects affected / exposed occurrences (all)</p> <p>Erythema subjects affected / exposed occurrences (all)</p> <p>Rash subjects affected / exposed occurrences (all)</p> <p>Rash erythematous subjects affected / exposed occurrences (all)</p>	<p>2 / 21 (9.52%) 6</p> <p>2 / 21 (9.52%) 5</p> <p>2 / 21 (9.52%) 4</p> <p>2 / 21 (9.52%) 3</p> <p>1 / 21 (4.76%) 2</p> <p>2 / 21 (9.52%) 3</p> <p>0 / 21 (0.00%) 0</p>		
<p>Renal and urinary disorders</p> <p>Proteinuria subjects affected / exposed occurrences (all)</p>	<p>2 / 21 (9.52%) 4</p>		
<p>Musculoskeletal and connective tissue disorders</p>			

Back pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Amyotrophy			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Bronchitis			

subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
<b>Nasopharyngitis</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
<b>Rhinitis</b>			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
<b>Lung infection</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
<b>Urinary tract infection</b>			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	2		
<b>Tooth abscess</b>			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
<b>Conjunctivitis</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
<b>Infection</b>			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
<b>Metabolism and nutrition disorders</b>			
<b>Myalgia</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
<b>Decreased appetite</b>			
subjects affected / exposed	7 / 21 (33.33%)		
occurrences (all)	16		
<b>Hypercreatinaemia</b>			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	5		
<b>Hyperkalaemia</b>			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		

Hyperglycaemia			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Malnutrition			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2013	<ul style="list-style-type: none"><li>- addition of an evaluation of the quality of life</li><li>- reduction of the number of sites</li><li>- addition of an inclusion criteria regarding the measurability of the disease</li><li>- clarification of inclusion and exclusion criteria</li><li>- clarification on the use of anticoagulation during the trial</li><li>- deletion of the biological study</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Patients included in the DOC arm tended to be older and to be more frequently never smokers than in the paclitaxel-bavacizumab arm.  
Cross-over from one arm to another prevented any definitive conclusion on OS benefit.

Notes:

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### Online references

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