



## Clinical trial results:

### A phase II study of geriatric assessment as screening criterion and predictive factor for safety in elderly patients ( 70 years) with non-small-cell lung cancer candidates for treatment with bevacizumab, carboplatin and paclitaxel

#### Summary

EudraCT number	2012-002452-16
Trial protocol	ES
Global end of trial date	29 September 2017

#### Results information

Result version number	v1 (current)
This version publication date	22 September 2022
First version publication date	22 September 2022
Summary attachment (see zip file)	GIDO1201 (Gido1201-final-2017.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	GIDO1201
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##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	GIDO (Grup d'investigació i divulgació oncológica)
Sponsor organisation address	Velazquez 7 - 3ª, Madrid, Spain, 28001
Public contact	GIDO, GIDO, secretariado@gido.es
Scientific contact	GIDO, GIDO , secretariado@gido.es

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

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety of bevacizumab in combination with carboplatin and paclitaxel as first-line treatment in elderly patients ( $\geq 70$  years) with non-small-cell lung cancer, in terms of grade 3-4 neutropenia.

Protection of trial subjects:

This clinical trial was conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki on medical research in human subjects (59th WMA General Assembly, Seoul, Korea, 2008), and in accordance with applicable regulatory requirements, in particular the 1996 ICH Harmonised Tripartite Guidelines For Good Clinical Practice and Royal Decree 223/2004 regulating clinical trials with medicinal products in Spain at the time of study initiation, and incorporating all the specific provisions for application in the member states of European Directive 2001/20/EC on clinical trials on medicinal products for human use.

By signing this protocol, the investigators agreed to follow the instructions and procedures described in the protocol and therefore to comply with the principles of GCP on which it is based.

Each patient who was asked to participate in the study was given a written document called "Patient Information Sheet", which contained the necessary relevant information about the nature of the study, the study objectives and procedures, the potential benefits and risks for the patient, and the guarantee to protect his/her data. In addition, this document stated the voluntary nature of participation of the patient in the study and indicated in a clear and unequivocal manner the possibility of refusing to participate and withdrawing his/her consent at any time and for any reason, without having to explain this decision, and without it affecting his/her treatment and subsequent medical follow-up or his/her relationship with the physician treating him/her.

Prior to the conduct of this study and in compliance with Royal Decree 223/2004, the sponsor submitted the protocol and informed consent form along with the pertinent documentation to the reference Clinical Research Ethics Committee (CREC) for its evaluation and subsequent report.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

Notes:

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**Subjects enrolled per age group**

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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)	0
From 65 to 84 years	27
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

The patients were included in the study between 28-8-2013 and 30-06-2015.

### Pre-assignment

Screening details:

Patients with  $\geq 70$  years of age, with a histologically or cytologically confirmed diagnosis of nonsquamous NSCLC with EGFR gene mutational status negative, with stage IV disease, with ECOG performance score of 0-1, and adequate bone marrow and renal function who have not received first-line treatment.

### Period 1

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

### Arms

Arm title	Single arm
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Arm description:

Patients included in the clinical trial received an initial treatment formed by the combination of bevacizumab, carboplatin and paclitaxel for 4-6 cycles (at the investigator's discretion) of 21 days, followed by maintenance treatment with bevacizumab monotherapy until disease progression or premature withdrawal of the patient from the study for any reason, including unacceptable toxicity, or until patient death.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

Bevacizumab was administered by intravenous infusion at a dose of 7.5 mg/kg (per body weight) on day 1 of each 21-day cycle in combination with carboplatin and paclitaxel for 4-6 cycles (at the investigator's discretion) of treatment. In the absence of disease progression or unacceptable toxicity, treatment was maintained with bevacizumab monotherapy until disease progression or unacceptable toxicity, which was administered on day 1 of each 21-day cycle.

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

Dosage and administration details:

Carboplatin was administered by intravenous infusion on day 1 of each 21-day cycle for 4-6 cycles (at the investigator's discretion) in combination with paclitaxel and bevacizumab. The dose of carboplatin (mg) was determined using the Calvert formula:  $\text{Dose (mg)} = \text{target AUC (mg/mL} \times \text{min)} \times [\text{GFR mL/min} + 25]$ . The target AUC was 4 mg/min/mL. The Calvert formula was not be used in patients who had previously received intensive treatment.

Investigational medicinal product name	Paclitaxel
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:

Paclitaxel was administered by intravenous infusion at a dose of 175 mg/m<sup>2</sup> on day 1 of each 21-day cycle for 4-6 cycles (at the investigator's discretion) in combination with carboplatin and bevacizumab. Doses of paclitaxel were based on calculation of the patient's body surface area, according to measurements of the patient's weight and height taken on each visit. Body surface area (BSA) had to be calculated using a standard nomogram.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Single arm
Started	26
Completed	26

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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: One patient was considered a screening failure and did not receive treatment, and was thus not included in the ITT population or safety population. Consequently, 26 patients received treatment and were included in the ITT population and the Safety population.

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
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Reporting group description:

The population analysed is defined below:

Population by Intention-to-Treat (ITT): Includes the patients treated; that is, those that received at least one dose of any of the study drugs.

At the time of the database cut-off (29-09-2017) 27 recruited patients were available, of which one was a screening failure for not meeting the selection criteria and did not receive treatment.

Therefore, the final number of patient analysed and that formed part of the ITT population was 26 patients.

Reporting group values	Overall trial	Total	
Number of subjects	26	26	
Age categorical			
Elderly patients ( $\geq 70$ years) diagnosed with advanced non-squamous non-small-cell lung cancer.			
Units: Subjects			
Under 70 years	0	0	
From 70-84 years	26	26	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	76.7		
standard deviation	$\pm 4.2$	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	20	20	
Smoking status			
Units: Subjects			
Active smoker	6	6	
Ex-smoker	13	13	
Non-smoker	7	7	
ECOG			
Units: Subjects			
ECOG 0	6	6	
ECOG 1	20	20	
Katz scale			
Units: Subjects			
Five	2	2	
Six	24	24	
Simplified Lawton scale			
Units: Subjects			
Three	1	1	
Four	2	2	
Five	8	8	
Six	15	15	
Charlson comorbidity index			

Units: Subjects			
Zero	5	5	
One	6	6	
Two	8	8	
Three	7	7	
Geriatric syndromes			
Units: Subjects			
Depression	1	1	
Falls	1	1	
Dementia	0	0	
Delirium	0	0	
Abandonment, mistreatment	0	0	
Spontaneous fractures	0	0	
None	24	24	
Surgical resection of the primary tumor			
Units: Subjects			
Yes	3	3	
No	23	23	
Radiotherapy			
Units: Subjects			
Yes	1	1	
No	25	25	
Technique used for confirmation of diagnosis of advanced/metastatic disease			
Units: Subjects			
Histologic (biopsy)	18	18	
Cytological (FNPA)	5	5	
Histologic + cytological	3	3	
Site of metastases, local/regional			
Units: Subjects			
Yes	10	10	
No	16	16	
Site of metastases, bone			
Units: Subjects			
Yes	8	8	
No	18	18	
Site of metastases, liver			
Units: Subjects			
Yes	6	6	
No	20	20	
Site of metastases, pleura			
Units: Subjects			
Yes	6	6	
No	20	20	
Site of metastases, adrenal gland			
Units: Subjects			
Yes	4	4	
No	22	22	
Site of metastases, brain			
Units: Subjects			
Yes	4	4	

No	22	22	
Site of metastases, adenopathies Units: Subjects			
Yes	4	4	
No	22	22	
Sites of target and non-target lesions, lung Units: Subjects			
Yes	26	26	
No	0	0	
Sites of target and non-target lesions, lymphatic system Units: Subjects			
Yes	19	19	
No	7	7	
Sites of target and non-target lesions, bone Units: Subjects			
Yes	9	9	
No	17	17	
Sites of target and non-target lesions, liver Units: Subjects			
Yes	8	8	
No	18	18	
Sites of target and non-target lesions, adrenal gland Units: Subjects			
Yes	4	4	
No	22	22	
Sites of target and non-target lesions, kidney Units: Subjects			
Yes	3	3	
No	23	23	
Sites of target and non-target lesions, spleen Units: Subjects			
Yes	2	2	
No	24	24	
Number of organs with metastasis Units: Subjects			
1 organ	2	2	
2 organs	10	10	
3 organs	8	8	
>3 organs	6	6	
Number of metastatic lesions Units: Subjects			
2 lesions	1	1	
3 lesions	3	3	
4 lesions	5	5	
5 lesions	5	5	
6 lesions	3	3	

7 lesions	3	3	
>7 lesions	6	6	

Weight Units: Kg arithmetic mean standard deviation	69.5 ± 10.4	-	
Height Units: cm arithmetic mean standard deviation	162.5 ± 9.0	-	
No. years smoking Units: years arithmetic mean standard deviation	50.2 ± 14.7	-	
Body Mass Index (BMI) Units: Kg/m <sup>2</sup> arithmetic mean standard deviation	26.4 ± 3.7	-	
Comorbidity index Units: score arithmetic mean standard deviation	7.5 ± 4.5	-	
No. of medications Units: number arithmetic mean standard deviation	6.1 ± 3.6	-	
Folstein Mini-Mental Scale Units: score arithmetic mean standard deviation	31.0 ± 4.1	-	
Geriatric depression scale Units: score arithmetic mean standard deviation	1.1 ± 1.3	-	
Percentage of involuntary weight loss Units: percentaje arithmetic mean standard deviation	2.0 ± 4.3	-	
Albumin Units: g/dL arithmetic mean standard deviation	3.5 ± 1.2	-	
Time since diagnosis of NSCLC Units: years arithmetic mean standard deviation	4.1 ± 9.3	-	
Time since diagnosis Units: years arithmetic mean standard deviation	1.7 ± 2.5	-	

Number of organs with metastasis (mean) Units: number arithmetic mean standard deviation	2.9 ± 1.3	-	
Number of metastatic lesions (mean) Units: number arithmetic mean standard deviation	5.9 ± 2.5	-	

## End points

### End points reporting groups

Reporting group title	Single arm
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Reporting group description:

Patients included in the clinical trial received an initial treatment formed by the combination of bevacizumab, carboplatin and paclitaxel for 4-6 cycles (at the investigator's discretion) of 21 days, followed by maintenance treatment with bevacizumab monotherapy until disease progression or premature withdrawal of the patient from the study for any reason, including unacceptable toxicity, or until patient death.

### Primary: Rate of grade 3-4 neutropenia related with the treatment

End point title	Rate of grade 3-4 neutropenia related with the treatment <sup>[1]</sup>
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End point description:

The primary endpoint of the study will be the rate of grade 3-4 neutropenia, defined according to the National Cancer Institute Common Terminology Criteria the National Cancer Institute Common Terminology Criteria version 4.0 (NCI-CTC v4.0).

It will be assessed from the first administration of study treatment until 28 ± 3 days after completion/interruption of treatment.

End point type	Primary
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End point timeframe:

Since August 2013 (start of recruitment) until study closure (at 12 months from inclusion of the last patient in the study).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a single-arm study. No comparative analyses were planned for this endpoint (only descriptive statistics).

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: percentage				
number (confidence interval 95%)	3.8 (0.2 to 21.6)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS)

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

Time elapsed from the start of treatment to the treatment to the date on which disease progression according to RECIST v1.1 criteria or death from any cause is documented. RECIST v1.1 criteria or death from any cause.

End point type	Secondary
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End point timeframe:

Since August 2013 (start of recruitment) until study closure (at 12 months from inclusion of the last

patient in the study).

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<b>End point values</b>	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: months				
median (confidence interval 95%)	8.2 (5.2 to 11.2)			

### Statistical analyses

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No statistical analyses for this end point

#### Secondary: Overall survival (OS)

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End point title	Overall survival (OS)
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End point description:

Time elapsed from the start of treatment to the time of death of the patient, regardless of the length of time the patient received the study treatment and the cause of death. treatment and the cause of death, regardless of how long the patient received the study treatment and the cause of death.

End point type	Secondary
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End point timeframe:

Since August 2013 (start of recruitment) until study closure (at 12 months from inclusion of the last patient in the study).

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<b>End point values</b>	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: months				
median (confidence interval 95%)	12.6 (9.3 to 15.9)			

### Statistical analyses

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No statistical analyses for this end point

#### Secondary: Objective response rate (ORR)

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End point title	Objective response rate (ORR)
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End point description:

The objective response rate is defined as complete response (CR) + partial response (PR), according to the Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST v1.1). Therefore, tumor response will be assessed at the screening visit (within 28 days prior to study treatment administration). In the treatment phase, it will be evaluated in cycles 2 and 4 of the initial carboplatin combination In the initial carboplatin-paclitaxel-bevacizumab combination treatment phase; then, in the maintenance

treatment phase with bevacizumab monotherapy, it will be evaluated every 3 cycles (63 days) until disease progression, unacceptable toxicity or premature abandonment for any cause. Subsequently, at the end-of-treatment visit (28 ± 3 days after completion/interruption of study medication) and at follow-up visits (every 3 months ± 3 weeks).

End point type	Secondary
End point timeframe:	
Since August 2013 (start of recruitment) until study closure (at 12 months from inclusion of the last patient in the study).	

<b>End point values</b>	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: percentage				
number (confidence interval 95%)				
Objective response rate (CR +PR)	34.6 (17.9 to 55.6)			
Tumor control rate (CR+PR+SD)	88.5 (68.7 to 97.0)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Best response to treatment

End point title	Best response to treatment
End point description:	
Best confirmed response to treatment according to the Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST v1.1).	
End point type	Secondary
End point timeframe:	
Since August 2013 (start of recruitment) until study closure (at 12 months from inclusion of the last patient in the study).	

<b>End point values</b>	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: patients				
Complete response (CR)	0			
Partial response (PR)	9			
Stable disease (SD)	14			
Progressive disease (PD)	3			

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Since August 2013 (start of recruitment) until study closure (at 12 months from inclusion of the last patient in the study).

Adverse event reporting additional description:

It is the investigator's responsibility to report all AAGs in the CRD, whether observed by the investigator or spontaneously reported by the patient participating in the study, regardless of the relationship to the treatments. AAGs will also be reported immediately to the CRO by the investigator using the AAG Reporting Form.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

### Reporting groups

Reporting group title	Single arm
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Reporting group description:

Patients included in the clinical trial received an initial treatment formed by the combination of bevacizumab, carboplatin and paclitaxel for 4-6 cycles (at the investigator's discretion) of 21 days, followed by maintenance treatment with bevacizumab monotherapy until disease progression or premature withdrawal of the patient from the study for any reason, including unacceptable toxicity, or until patient death.

<b>Serious adverse events</b>	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 26 (53.85%)		
number of deaths (all causes)	24		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral hemorrhage			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis ischaemic			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary sepsis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 26 (19.23%)		
occurrences (all)	17		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Mucosal inflammation			

subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 5		
Oedema subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 9		
Asthenia subjects affected / exposed occurrences (all)	20 / 26 (76.92%) 44		
Pyrexia subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 7		
Respiratory, thoracic and mediastinal disorders			
Dysphonia subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 6		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Epistaxis subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 10		
Dyspnoea subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 7		
Cough subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 9		
Pulmonary embolism subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3		
Injury, poisoning and procedural complications			

<p>Infusion related reaction  subjects affected / exposed  occurrences (all)</p>	<p>2 / 26 (7.69%)  3</p>		
<p>Nervous system disorders</p> <p>Headache  subjects affected / exposed  occurrences (all)</p> <p>Dysgeusia  subjects affected / exposed  occurrences (all)</p> <p>Dizziness  subjects affected / exposed  occurrences (all)</p> <p>Neurotoxicity  subjects affected / exposed  occurrences (all)</p> <p>Paraesthesia  subjects affected / exposed  occurrences (all)</p> <p>Tremor  subjects affected / exposed  occurrences (all)</p>	<p>2 / 26 (7.69%)  2</p> <p>4 / 26 (15.38%)  4</p> <p>3 / 26 (11.54%)  3</p> <p>11 / 26 (42.31%)  19</p> <p>2 / 26 (7.69%)  2</p> <p>2 / 26 (7.69%)  2</p>		
<p>Blood and lymphatic system disorders</p> <p>Anemia  subjects affected / exposed  occurrences (all)</p> <p>Neutropenia  subjects affected / exposed  occurrences (all)</p> <p>Febrile neutropenia  subjects affected / exposed  occurrences (all)</p>	<p>10 / 26 (38.46%)  24</p> <p>2 / 26 (7.69%)  2</p> <p>2 / 26 (7.69%)  2</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain  subjects affected / exposed  occurrences (all)</p> <p>Diarrhea</p>	<p>3 / 26 (11.54%)  3</p>		

subjects affected / exposed occurrences (all)	9 / 26 (34.62%) 14		
Constipation subjects affected / exposed occurrences (all)	7 / 26 (26.92%) 9		
Nausea subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 5		
Vomiting subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 8		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	12 / 26 (46.15%) 15		
Dry skin subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3		
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 4		
Musculoskeletal and connective tissue disorders			
Spinal pain subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Back pain subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 6		
Pain in extremity subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3		
Arthralgia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	10 / 26 (38.46%) 14		
Hypocalcemia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2013	Change of principal investigator of Hospital de Sagunto (Valencia).
08 October 2014	Inclusion of new sites. A site is added: Hospital Lluís Alcanyis de Xàtiva.
08 October 2014	Inclusion of new sites. Two sites are added: Hospital General de Alicante and Hospital General de Valencia.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported