



Clinical trial results:

Phase II study in patient in first line for HER - metastasis breast cancer treated with eribulin and bevacizumab

Summary

EudraCT number	2013-001710-15
Trial protocol	FR
Global end of trial date	26 February 2019

Results information

Result version number	v1 (current)
This version publication date	16 August 2023
First version publication date	16 August 2023

Trial information

Trial identification

Sponsor protocol code	GINECO-BR110
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ARCAGY-GINECO
Sponsor organisation address	8 rue Lamennais , Paris, France, 75008
Public contact	MARMION, ARCAGY-GINECO, 33 1 42348323,
Scientific contact	MARMION, ARCAGY-GINECO, 33 1 42348323,

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	10 June 2017
Is this the analysis of the primary completion data?	No
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Global end of trial reached?	Yes
Global end of trial date	26 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the proportion of non-progressive patients at 1 year (disease control rate or non-progression rate at 12 months)

Protection of trial subjects:

This study was conducted according to the recommendations then in effect:

- the Huriel law (n°88-1138) of December 20, 1988 relating to the Protection of Persons taking part in Biomedical Research and amended by the public health law (n°2004-806) of August 9, 2004,
- the Data Protection Act No. 78-17 amended by Law No. 2004-801 of August 6, 2004 on the protection of individuals with regard to the processing of personal data,
- the Bioethics law n° 2004-800 of August 6, 2004,
- good clinical practices from the international harmonization conference (ICH-E6 of 07/17/1996),
- European direction (2001/20/EC) on the conduct of clinical trials.

Before the start of the study, the protocol and the related documents (patient information, consent form, investigators brochure) were submitted for review by the National Agency for the Safety of Medicines and Health Products (ANSM) and the Committee for the Protection of Persons (CPP) Ile de France 1.

They obtained authorization from the ANSM on 07/19/2013 and the favorable opinion of the CPP Ile de France 1 on 06/11/2013.

Background therapy:

The efficacy of eribulin is well established in patients with metastatic breast cancer previously treated with taxanes and anthracyclines. The Embrace study found a response rate of 12% in multi-treated patients refractory to the last line of chemotherapy. The benefit is comparable in patients refractory or not to taxanes, and pretreated or not with capecitabine. We can therefore expect a response rate at least equivalent in first-line metastatic treatment to that of taxanes or capecitabine. Phase II of eribulin (36) in first line goes in this direction because it highlights a response rate comparable to that found in first line.

line with paclitaxel in the study by K Miller (32): 27.1% versus 21% with a strictly identical PFS.

Adding bevacizumab to paclitaxel increased the response rate from 21% to 37% and the PFS from 5.9 to 11.8 months. The phase III chemotherapy combinations with bevacizumab all showed a benefit in favor of the combination in terms of response rate and PFS.

Eribulin is a cytotoxic agent with a mode of action very similar to paclitaxel by inhibiting microtubules. We can expect its association with bevacizumab to increase its efficacy in terms of response rate and PFS in the same way as with all the other cytotoxic drugs studied and particularly paclitaxel. The toxicity profile of eribulin is very close to that of paclitaxel, essentially neuropathy and hematotoxicity, but phase II suggests a better therapeutic index with a lower rate of neuropathy (12.5% grade 3-4 versus 17% with paclitaxel).

Evidence for comparator:

It therefore seems particularly interesting to study the efficacy and tolerance of the combination of eribulin and bevacizumab in first-line metastatic treatment in Her2-negative breast cancer. All the cytotoxic agents associated with bevacizumab in the various phase III were at their recommended dose in monotherapy and in particular the dose in the Marketing Authorization recommended for paclitaxel in

combination with bevacizumab is that of monotherapy. This is justified by the absence of cross-toxicity between cytotoxics and bevacizumab. The ESMERALDA study will therefore focus on the combination of bevacizumab and eribulin, at the recommended doses as monotherapy, with dose reduction in the event of toxicity. In the paclitaxel bevacizumab combination, the disease control rate at one year is 50%, which will therefore be considered as a promising rate and the reference for the statistical calculation of the sample in our study.

Actual start date of recruitment	13 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	41
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 62 patients were enrolled between September 2013 and September 2014.

Pre-assignment

Screening details:

One patient withdrew consent before receiving treatment, therefore the intention-to-treat population included 61 treated patients.

Period 1

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

Arms

Arm title	Bevacizumab + Eribulin
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Arm description:

A total of 62 patients were enrolled. One patient withdrew consent before receiving treatment, therefore the intention-to-treat population included 61 treated patients.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg at D1

The cycles were repeated every 3 weeks (D1=D22).

Bevacizumab treatment was continued until progression or intolerable toxicity.

Investigational medicinal product name	Eribuline
Investigational medicinal product code	
Other name	Halaven
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1,23 mg/m² at D1 and at D8

The cycles were repeated every 3 weeks (D1=D22).

Eribulin treatment was administered for up to 6 cycles or until progression as long as the benefit/risk ratio was considered favorable for the patient.

Number of subjects in period 1	Bevacizumab + Eribulin
Started	62
Completed	61
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups

Reporting group title	Overall period
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Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	62	62	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	41	41	
From 65-84 years	21	21	
85 years and over	0	0	
Age continuous			
Units: years			
median	59		
full range (min-max)	38 to 77	-	
Gender categorical			
Units: Subjects			
Female	62	62	
Histological grade at diagnosis			
Units: Subjects			
01	6	6	
02	31	31	
03	21	21	
Unknown	3	3	
Patient withdrawn consent	1	1	
Prior chemotherapy			
Units: Subjects			
Neoadjuvant	12	12	
Adjuvant	31	31	
NA	19	19	
Prior radiotherapy			
Units: Subjects			
Prior radiotherapy	48	48	
NA	14	14	
Prior endocrine therapy			
Units: Subjects			
For metastatic disease	22	22	
Other	18	18	
NA	22	22	

ECOG performance status at inclusion Units: Subjects			
00	35	35	
01	25	25	
Unknown	1	1	
Patient withdrawn consent	1	1	
De novo metastatic disease Units: Subjects			
De novo metastatic disease	13	13	
NA	49	49	
Number of metastatic sites Units: Subjects			
01	21	21	
02	22	22	
≥3	18	18	
Patient withdrawn consent	1	1	
Receptor status at diagnosis: Estrogen receptor positive Units: Subjects			
Estrogen receptor positive	47	47	
NA	15	15	
Receptor status at diagnosis: Progesterone receptor positive Units: Subjects			
Progesterone receptor positive	34	34	
NA	28	28	
Receptor status at diagnosis: Triple negative Units: Subjects			
Triple negative	10	10	
NA	52	52	
Metastatic sites: Liver Units: Subjects			
Liver	25	25	
NA	37	37	
Metastatic sites: Lung Units: Subjects			
Lung	23	23	
NA	39	39	
Metastatic sites: Pleura Units: Subjects			
Pleura	5	5	
NA	57	57	
Metastatic sites: Bone Units: Subjects			
Bone	34	34	
NA	28	28	
Metastatic sites: Lymph nodes Units: Subjects			
Lymph nodes	21	21	
NA	41	41	
Type of (neo)adjuvant chemotherapy:			

Paclitaxel Units: Subjects			
Paclitaxel	4	4	
NA	58	58	
Type of (neo)adjuvant chemotherapy: Docetaxel Units: Subjects			
Docetaxel	30	30	
NA	32	32	
Type of (neo)adjuvant chemotherapy: Anthracycline Units: Subjects			
Anthracycline	38	38	
NA	24	24	
Type of (neo)adjuvant chemotherapy: Cyclophosphamide Units: Subjects			
Cyclophosphamide	39	39	
NA	23	23	
Type of (neo)adjuvant chemotherapy: 5-FU Units: Subjects			
5-FU	32	32	
NA	30	30	
Histologic subtype at diagnosis: Ductal Units: Subjects			
Ductal	54	54	
NA	8	8	
Histologic subtype at diagnosis: Lobular Units: Subjects			
Lobular	5	5	
NA	57	57	
Histologic subtype at diagnosis: Mucinous Units: Subjects			
Mucinous	1	1	
NA	61	61	
Histologic subtype at diagnosis: Tubulo- lobular Units: Subjects			
Tubulo-lobular	1	1	
NA	61	61	

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A total of 62 patients were recruited between September 2013 and September 2014. One patient withdrew consent prior to receiving treatment, therefore, the intent-to-treat population comprised 61 treated patients. Among these, one patient changed treatment before 12 months despite stable disease, thus the evaluable population for the primary endpoint comprised 60 patients.

Reporting group values	ITT population		
Number of subjects	61		
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)	41		
From 65-84 years	21		
85 years and over	0		
Age continuous			
Units: years			
median	59		
full range (min-max)	38 to 77		
Gender categorical			
Units: Subjects			
Female	61		
Histological grade at diagnosis			
Units: Subjects			
01	6		
02	31		
03	21		
Unknown	3		
Patient withdrawn consent	1		
Prior chemotherapy			
Units: Subjects			
Neoadjuvant	12		
Adjuvant	31		
NA	19		
Prior radiotherapy			
Units: Subjects			
Prior radiotherapy	48		
NA	14		
Prior endocrine therapy			
Units: Subjects			
For metastatic disease	22		
Other	18		
NA	22		
ECOG performance status at inclusion			
Units: Subjects			
00	35		
01	25		
Unknown	1		
Patient withdrawn consent	1		
De novo metastatic disease			
Units: Subjects			

De novo metastatic disease	13		
NA	49		
Number of metastatic sites			
Units: Subjects			
01	21		
02	22		
≥3	18		
Patient withdrawn consent	1		
Receptor status at diagnosis: Estrogen receptor positive			
Units: Subjects			
Estrogen receptor positive	47		
NA	15		
Receptor status at diagnosis: Progesterone receptor positive			
Units: Subjects			
Progesterone receptor positive	34		
NA	28		
Receptor status at diagnosis: Triple negative			
Units: Subjects			
Triple negative	10		
NA	52		
Metastatic sites: Liver			
Units: Subjects			
Liver	25		
NA	37		
Metastatic sites: Lung			
Units: Subjects			
Lung	23		
NA	39		
Metastatic sites: Pleura			
Units: Subjects			
Pleura	5		
NA	57		
Metastatic sites: Bone			
Units: Subjects			
Bone	34		
NA	28		
Metastatic sites: Lymph nodes			
Units: Subjects			
Lymph nodes	21		
NA	41		
Type of (neo)adjuvant chemotherapy: Paclitaxel			
Units: Subjects			
Paclitaxel	4		
NA	58		
Type of (neo)adjuvant chemotherapy: Docetaxel			
Units: Subjects			
Docetaxel	30		
NA	32		

Type of (neo)adjuvant chemotherapy: Anthracycline Units: Subjects			
Anthracycline	38		
NA	24		
Type of (neo)adjuvant chemotherapy: Cyclophosphamide Units: Subjects			
Cyclophosphamide	39		
NA	23		
Type of (neo)adjuvant chemotherapy: 5-FU Units: Subjects			
5-FU	32		
NA	30		
Histologic subtype at diagnosis: Ductal Units: Subjects			
Ductal	54		
NA	8		
Histologic subtype at diagnosis: Lobular Units: Subjects			
Lobular	5		
NA	57		
Histologic subtype at diagnosis: Mucinous Units: Subjects			
Mucinous	1		
NA	61		
Histologic subtype at diagnosis: Tubulo- lobular Units: Subjects			
Tubulo-lobular	1		
NA	61		

End points

End points reporting groups

Reporting group title	Bevacizumab + Eribulin
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Reporting group description:

A total of 62 patients were enrolled. One patient withdrew consent before receiving treatment, therefore the intention-to-treat population included 61 treated patients.

Subject analysis set title	ITT population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

A total of 62 patients were recruited between September 2013 and September 2014. One patient withdrew consent prior to receiving treatment, therefore, the intent-to-treat population comprised 61 treated patients. Among these, one patient changed treatment before 12 months despite stable disease, thus the evaluable population for the primary endpoint comprised 60 patients.

Primary: The 1-year non-progression rate

End point title	The 1-year non-progression rate ^[1]
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End point description:

Based on a Simon's two stage design to detect with $\alpha = 0.05$ and a power of 80%, a PFS at 1-year rate of 50% (not reached).

At the data cutoff, disease progression or death had been recorded in 58 (95%) of the 61 treated patients. The 1-year non-progression rate was 32% (95% confidence interval [CI]: 20-43%).

End point type	Primary
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End point timeframe:

Overall trial

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: Trial's methodology is based on a Simon's two step design. Results are given with 95% Confidence Interval.

This endpoint was chosen to provide a clear threshold rapidly and reliably in a single-arm study.

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: percent				
number (confidence interval 95%)				
The 1-year non-progression rate (%)	32 (20 to 43)			

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:

At the data cutoff, disease progression or death had been recorded in 58 (95%) of the 61 treated patients. The 1-year non-progression rate was 32% (95% confidence interval [CI]: 20-43%). The ORR in 59 evaluable patients was 47% (95% CI: 34-60%), including complete response in six patients (10%). Median PFS was 8.3 months (95% CI: 7.0-9.6 months)

End point type	Secondary
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End point timeframe:

Overall trial

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: month				
median (confidence interval 95%)				
Progression-free survival (PFS)	8.3 (7.0 to 9.6)			

Attachments (see zip file)	Figure 1 - Progression-free survival.JPG
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

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

End point type	Secondary
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End point timeframe:

Overall trial

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: month				
median (confidence interval 95%)				
Overall survival (OS)	28.3 (22.8 to 33.9)			

Attachments (see zip file)	Figure 2 - Overall survival (OS)/Figure 2 - Overall survival.JPG
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Statistical analyses

No statistical analyses for this end point

Secondary: Baseline visual analog scale (VAS) score

End point title	Baseline visual analog scale (VAS) score
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End point description:

End point type	Secondary
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End point timeframe:

Overall trial

End point values	Bevacizumab + Eribulin			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: number				
arithmetic mean (standard deviation)				
Visual analog scale (VAS) score	6.55 (\pm 2.20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cycle 4 visual analog scale (VAS) score

End point title	Cycle 4 visual analog scale (VAS) score
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End point description:

A baseline VAS score was available in 60 of the 62 patients enrolled. The mean score was 6.55 (standard deviation [SD] 2.20).

At cycle 4, 38 patients reported a VAS score. The mean score at cycle 4 was 6.66 (SD 2.16), showing no deterioration of quality of life with treatment.

End point type	Secondary
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End point timeframe:

Overall trial

End point values	Bevacizumab + Eribulin			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: number				
arithmetic mean (standard deviation)				
Cycle 4 VAS score	6.66 (\pm 2.16)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	ITT population
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Reporting group description: -

Serious adverse events	ITT population		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 61 (47.54%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Radiomucositis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertention			
subjects affected / exposed	8 / 61 (13.11%)		
occurrences causally related to treatment / all	9 / 11		
deaths causally related to treatment / all	0 / 0		
Arterial hypertension			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Leg vein thrombosis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Surgical and medical procedures			
Appendectomy			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile aplasia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right arm and breast pain			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Aspecific colitis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Sub acute pulmonary edema			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Left ankle ulcer			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteo-chemo necrosis of the jaw			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septicemia			

subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious syndrome			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious syndrome with no obvious point of appeal			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ITT population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 61 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	50 / 61 (81.97%)		
occurrences (all)	50		
Edema			
subjects affected / exposed	13 / 61 (21.31%)		
occurrences (all)	13		
Arterial ischemia			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	47 / 61 (77.05%)		
occurrences (all)	47		
Fatigue			
subjects affected / exposed	45 / 61 (73.77%)		
occurrences (all)	45		

Headache			
subjects affected / exposed	18 / 61 (29.51%)		
occurrences (all)	18		
Fever			
subjects affected / exposed	9 / 61 (14.75%)		
occurrences (all)	9		
Dysphonia			
subjects affected / exposed	8 / 61 (13.11%)		
occurrences (all)	8		
Cough			
subjects affected / exposed	7 / 61 (11.48%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	12 / 61 (19.67%)		
occurrences (all)	12		
Rhinitis			
subjects affected / exposed	9 / 61 (14.75%)		
occurrences (all)	9		
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Product issues			
Mucositis			
subjects affected / exposed	16 / 61 (26.23%)		
occurrences (all)	16		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences (all)	2		
Myocardial infarction			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Left ventricular ejection fraction (LVEF) decreased			

subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Nervous system disorders Paresthesia/dysesthesia subjects affected / exposed occurrences (all)	26 / 61 (42.62%) 26		
Peripheral motor neuropathy subjects affected / exposed occurrences (all)	15 / 61 (24.59%) 15		
Blood and lymphatic system disorders Leukocytopenia subjects affected / exposed occurrences (all)	44 / 61 (72.13%) 44		
Neutropenia subjects affected / exposed occurrences (all)	43 / 61 (70.49%) 43		
Lymphocytopenia subjects affected / exposed occurrences (all)	28 / 61 (45.90%) 28		
Anemia subjects affected / exposed occurrences (all)	26 / 61 (42.62%) 26		
Febrile neutropenia subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3		
Hemorrhage subjects affected / exposed occurrences (all)	22 / 61 (36.07%) 22		
Thrombosis subjects affected / exposed occurrences (all)	9 / 61 (14.75%) 9		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	23 / 61 (37.70%) 23		
Constipation			

subjects affected / exposed	23 / 61 (37.70%)		
occurrences (all)	23		
Diarrhea			
subjects affected / exposed	21 / 61 (34.43%)		
occurrences (all)	21		
Vomiting			
subjects affected / exposed	12 / 61 (19.67%)		
occurrences (all)	12		
Dysphagia			
subjects affected / exposed	3 / 61 (4.92%)		
occurrences (all)	3		
Appendicitis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Colitis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences (all)	1		
Hepatobiliary disorders			
GGT increased			
subjects affected / exposed	19 / 61 (31.15%)		
occurrences (all)	19		
Transaminase increased			
subjects affected / exposed	15 / 61 (24.59%)		
occurrences (all)	15		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	34 / 61 (55.74%)		
occurrences (all)	34		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	9 / 61 (14.75%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 61 (19.67%)		
occurrences (all)	12		

Myalgia subjects affected / exposed occurrences (all)	9 / 61 (14.75%) 9		
Cramp subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 7		
Osteonecrosis subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Infections and infestations Urinary infection subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 8		
Rhinopharyngitis subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 7		
Septicemia subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 8		
Weight loss subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 8		
Dysgeusia subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2013	Amendement 1

Notes:

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.

It's a single-arm design with no standard comparator
Lack of detailed information on the evolution/resolution of neuropathy over time, the heterogeneity of the patient population, and the relevance of this regimen in the context of emerging options

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33188992>