Clinical trial results:
A Randomized Phase III Study Of Low-Docetaxel Oxaliplatin, Capecitabine (Low-Tox) Vs Epirubicin, Oxaliplatin And Capecitabine (Eox) In Patients With Locally Advanced Unresectable Or Metastatic Gastric Cancer

Summary

EudraCT number	2011-005537-39
Trial protocol	IT
Global end of trial date	31 December 2018

Results information

Result version number	v1 (current)
This version publication date	14 November 2019
First version publication date	14 November 2019
Summary attachment (see zip file)	LEGA Clinical Study Results (LEGA Clinical Study Results_final.pdf)

Trial information

Trial identification

Sponsor protocol code	LEGA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02076594
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione GISCAD
Sponsor organisation address	Via Gattinoni, 4, Vanzago (MI), Italy, 20010
Public contact	SILVIA ROTA, Fondazione Giscad, +39 02 84968409, CENTROTRIALGISCAD@YAHOO.IT
Scientific contact	SILVIA ROTA, Fondazione Giscad, +39 02 84968409, CENTROTRIALGISCAD@YAHOO.IT

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	17 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2018
Global end of trial reached?	Yes
Global end of trial date	31 December 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the therapeutic efficacy of Docetaxel, Oxaliplatin and Capecitabine (low-TOX) vs. Epirubicin, Oxaliplatin and Capecitabine (EOX) as measured by the duration of Progression Free Survival (PFS)in patient with locally advanced/metastatic gastric cancer.

Protection of trial subjects:

Study Protocol foresees that therapies considered necessary for the patient's well being might be given at the discretion of the Investigator, i.e chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 169
Worldwide total number of subjects	169
EEA total number of subjects	169

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)	102
From 65 to 84 years	67

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study inclusion and exclusion criteria were assessed during the screening period, i.e within 28 days of study drug start. Recruitment was initiated in each country/at each site after respective legal and ethical approval.

Pre-assignment

Screening details:

169 patients were enrolled in the study. Among the whole enrolled population, five patients have never been treated so the total number of patients randomized and treated amounts to 164 units (82 per arm).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1

Arm description:

All patient treated with Docetaxel, Oxaliplatin and Capecitabine (low-TOX)

Arm type	Experimental
Investigational medicinal product name	Docetaxel + Oxaliplatin + Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

The treatment consisted of:
-Docetaxel administered at 35 mg/ m2, intravenous at days 1 and 8 by 1-hour infusion;
-Oxaliplatin administered at 80 mg/ m2, intravenous at day 1 by 2-hour infusion;
-Capecitabine administered at 750 mg/ m2 (oral tablets of 500 and 150 mg) x2 daily for 2 weeks, followed by one week rest.
Cycles were repeated every 3 weeks

Arm title	Arm 2

Arm description:

All patient treated with Epirubicin + Oxaliplatin +Capecitabine (EOX)

Arm type	Active comparator
Investigational medicinal product name	Epirubicin + Oxaliplatin +Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

The treatment consisted of:
-Epirubicin administered at 50 mg/ m2, intravenous on day 1 by 2-hour infusion;
-Oxaliplatin administered at 130 mg/ m2, intravenous on day 1 by 2-hour infusion.
-Capecitabine administered at 625 mg/ m2 (oral tablets of 500 and 150 mg) x2 daily for 3 weeks.
Cycles were repeated every 3 weeks.

Number of subjects in period 1[1]	Arm 1	Arm 2
Started	82	82
Completed	34	37
Not completed	48	45
Progression disease	23	14
Interruption in study drug administration for more	5	3
Physician decision	9	-
Investigator's decision	-	6
Consent withdrawn by subject	-	5
Initiation of new anticancer therapy	2	-
Toxicity	4	10
Death	1	3
Intercurrent illness	1	1
Patient's decision	2	3
Lost to follow-up	1	-

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: Among the whole enrolled population (169 patients), five patients have never been treated so the total number of patients randomized and treated amounts to 164 units (82 per arm).

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1
Reporting group description:	
All patient treated with Docetaxel, Oxaliplatin and Capecitabine (low-TOX)	
Reporting group title	Arm 2
Reporting group description:	
All patient treated with Epirubicin + Oxaliplatin +Capecitabine (EOX)	

Reporting group values	Arm 1	Arm 2	Total
Number of subjects	82	82	164
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	45	54	99
From 65-84 years	37	28	65
85 years and over	0	0	0
Age continuous Units: years			
median	64.0	61.0	
full range (min-max)	33.0 to 84.0	35.0 to 77.0	-
Gender categorical Units: Subjects			
Female	29	30	59
Male	53	52	105
ECOG Units: Subjects			
Zero	62	64	126
One	20	16	36
Missing	0	2	2
Disease Extent at Study Entry Units: Subjects			
Locally advanced unresectable	12	5	17
Metastatic	70	77	147
Histological disease classification Units: Subjects			
Diffuse	27	19	46
Intestinal	29	25	54
Mix	5	6	11
Other	19	28	47
Missing	2	4	6

Histopathological Grade Units: Subjects			
G1	1	1	2
G2	15	9	24
G3	34	51	85
G4	1	2	3
GX	9	1	10
Unknown	22	18	40
Type of Prior Therapies Regimen Units: Subjects			
Surgery Alone	19	14	33
Surgery + Chemotherapy	9	8	17
Radiotherapy	2	0	2
Surgery + Chemotherapy + Radiotherapy	4	1	5
Unknown/Not Done	48	59	107

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description:	
All patient treated with Docetaxel, Oxaliplatin and Capecitabine (low-TOX)	
Reporting group title	Arm 2
Reporting group description:	
All patient treated with Epirubicin + Oxaliplatin +Capecitabine (EOX)	
Subject analysis set title	All patient treated with Docetaxel + Oxaliplatin +Capecitabine
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Arm 1_All subject treated with Docetaxel + Oxaliplatin + Capecitabine (low-TOX)	
Subject analysis set title	All patient treate with Epirubicin + Oxaliplatin +Capecitabine
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Arm 2_All patient treated with Epirubicin + Oxaliplatin +Capecitabine	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
Progression Free Survival (PFS) was defined as the time from randomization to the date of local or regional progression, distant metastasis, second primary malignancy or death from any cause, whichever comes first.	
End point type	Primary
End point timeframe:	
The time from randomization to the date of local or regional progression, distant metastasis, second primary malignancy or death from any cause, whichever comes first.	

End point values	All patient treated with Docetaxel + Oxaliplatin +Capecitabine	All patient treate with Epirubicin + Oxaliplatin +Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	82		
Units: Months				
median (confidence interval 95%)	6.3 (5.0 to 7.8)	6.3 (5.0 to 8.1)		

Statistical analyses

Statistical analysis title	Survival curves comparison
Comparison groups	All patient treated with Docetaxel + Oxaliplatin +Capecitabine v All patient treate with Epirubicin + Oxaliplatin +Capecitabine

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.983
Method	Logrank

Notes:

[1] - Log-Rank Test stratified by performance status

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall Survival (OS) is defined as the time from randomization to the date of death from any cause. Subjects who have not died while on study or have been lost to follow up were consored at the last contact date.

End point type	Secondary

End point timeframe:

Overall Survival (OS) is defined as the time from randomization to the date of death or date when the patient is lastly known alive.

End point values	All patient treated with Docetaxel + Oxaliplatin +Capecitabine	All patient treate with Epirubicin + Oxaliplatin +Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	82		
Units: Months				
median (confidence interval 95%)	11.5 (8.6 to 15.0)	12.4 (9.1 to 19.2)		

Statistical analyses

Statistical analysis title	Survival curves comparison
Comparison groups	All patient treate with Epirubicin + Oxaliplatin +Capecitabine v All patient treated with Docetaxel + Oxaliplatin +Capecitabine
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.838
Method	Logrank

Notes:

[2] - Log-Rank test stratified by performance status

Secondary: Objective Response Rate (CR+PR)

End point title	Objective Response Rate (CR+PR)

End point description:

Objective tumor response rate (ORR) is defined as the number of subjects whose best response to treatment achieved during study is CR (completed response) or PR (partial response), as evaluated by

the RECIST 1.1 criteria, over the number of randomized patients.

End point type	Secondary

End point timeframe:

During all study period

End point values	All patient treated with Docetaxel + Oxaliplatin +Capecitabine	All patient treate with Epirubicin + Oxaliplatin +Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	82		
Units: percent				
number (confidence interval 95%)	24.4 (16.4 to 34.7)	32.9 (23.7 to 43.7)		

Statistical analyses

Statistical analysis title	Treatment response comparison

Statistical analysis description:

Analysis performed by Mantel-Haenszlel Chi-Square Test controlling for ECOG Performance Status

Comparison groups	All patient treated with Docetaxel + Oxaliplatin +Capecitabine v All patient treate with Epirubicin + Oxaliplatin +Capecitabine
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.209
Method	Mantel-Haenszel

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

Disease control rate (DCR) is defined as the number of subjects whose best response is CR (Complete Response) ,PR (Partial Response) or SD (Stable Disease) lasting = or > 12 weeks, over the number of randomized patients.

End point type	Secondary

End point timeframe:

During all study period

End point values	All patient treated with Docetaxel + Oxaliplatin +Capecitabine	All patient treate with Epirubicin + Oxaliplatin +Capecitabine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	82		
Units: percent				
number (confidence interval 95%)	67.1 (56.3 to 76.3)	68.3 (57.6 to 77.4)		

Statistical analyses

Statistical analysis title	Treatment response comparison
Statistical analysis description: Analysis performed by Mantel-Haenszel Chi-Square Test controlling for ECOG Performance Status	
Comparison groups	All patient treate with Epirubicin + Oxaliplatin +Capecitabine v All patient treated with Docetaxel + Oxaliplatin +Capecitabine
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.975
Method	Mantel-Haenszel

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During all study period and followed until 28 days after the last dose of investigational product.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Arm1
Reporting group description: -	
Reporting group title	Arm 2
Reporting group description: -	

Serious adverse events	Arm1	Arm 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 82 (29.27%)	15 / 82 (18.29%)	
number of deaths (all causes)	59	55	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombophlebitis superficial			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 82 (2.44%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 82 (1.22%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
generalized oedema			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 82 (2.44%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 82 (3.66%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			

subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 82 (3.66%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 82 (2.44%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 82 (2.44%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 82 (1.22%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Eyelid ptosis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 82 (4.88%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 82 (2.44%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 82 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 82 (2.44%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 82 (3.66%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	3 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neck pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Candidiasis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malnutrition			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm1	Arm 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 82 (95.12%)	74 / 82 (90.24%)	
Investigations			
Weight decreased			
subjects affected / exposed	8 / 82 (9.76%)	3 / 82 (3.66%)	
occurrences (all)	11	3	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	9 / 82 (10.98%)	4 / 82 (4.88%)	
occurrences (all)	24	5	
Neuropathy peripheral			
subjects affected / exposed	16 / 82 (19.51%)	15 / 82 (18.29%)	
occurrences (all)	36	36	
Paraesthesia			
subjects affected / exposed	3 / 82 (3.66%)	5 / 82 (6.10%)	
occurrences (all)	7	18	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 82 (24.39%)	28 / 82 (34.15%)	
occurrences (all)	49	71	
Leukopenia			
subjects affected / exposed	10 / 82 (12.20%)	21 / 82 (25.61%)	
occurrences (all)	22	47	
Lymphopenia			
subjects affected / exposed	4 / 82 (4.88%)	9 / 82 (10.98%)	
occurrences (all)	8	18	
Neutropenia			

subjects affected / exposed	18 / 82 (21.95%)	33 / 82 (40.24%)	
occurrences (all)	37	79	
Thrombocytopenia			
subjects affected / exposed	3 / 82 (3.66%)	10 / 82 (12.20%)	
occurrences (all)	6	19	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	39 / 82 (47.56%)	29 / 82 (35.37%)	
occurrences (all)	116	71	
Mucosal inflammation			
subjects affected / exposed	18 / 82 (21.95%)	6 / 82 (7.32%)	
occurrences (all)	39	9	
Oedema peripheral			
subjects affected / exposed	5 / 82 (6.10%)	3 / 82 (3.66%)	
occurrences (all)	8	3	
Pyrexia			
subjects affected / exposed	11 / 82 (13.41%)	9 / 82 (10.98%)	
occurrences (all)	16	10	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	8 / 82 (9.76%)	0 / 82 (0.00%)	
occurrences (all)	14	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 82 (21.95%)	17 / 82 (20.73%)	
occurrences (all)	31	35	
Constipation			
subjects affected / exposed	14 / 82 (17.07%)	13 / 82 (15.85%)	
occurrences (all)	23	20	
Diarrhoea			
subjects affected / exposed	38 / 82 (46.34%)	24 / 82 (29.27%)	
occurrences (all)	76	37	
Dyspepsia			
subjects affected / exposed	5 / 82 (6.10%)	2 / 82 (2.44%)	
occurrences (all)	6	2	
Dysphagia			

subjects affected / exposed	5 / 82 (6.10%)	2 / 82 (2.44%)	
occurrences (all)	9	6	
Nausea			
subjects affected / exposed	37 / 82 (45.12%)	31 / 82 (37.80%)	
occurrences (all)	72	61	
Vomiting			
subjects affected / exposed	25 / 82 (30.49%)	21 / 82 (25.61%)	
occurrences (all)	37	30	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 82 (8.54%)	3 / 82 (3.66%)	
occurrences (all)	10	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 82 (12.20%)	9 / 82 (10.98%)	
occurrences (all)	29	40	
Erythema			
subjects affected / exposed	12 / 82 (14.63%)	1 / 82 (1.22%)	
occurrences (all)	22	3	
Nail disorder			
subjects affected / exposed	5 / 82 (6.10%)	0 / 82 (0.00%)	
occurrences (all)	14	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	22 / 82 (26.83%)	9 / 82 (10.98%)	
occurrences (all)	54	31	
Rash			
subjects affected / exposed	8 / 82 (9.76%)	1 / 82 (1.22%)	
occurrences (all)	14	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 82 (2.44%)	5 / 82 (6.10%)	
occurrences (all)	2	7	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	19 / 82 (23.17%)	11 / 82 (13.41%)	
occurrences (all)	44	19	
Hypocalcaemia			
subjects affected / exposed	6 / 82 (7.32%)	1 / 82 (1.22%)	
occurrences (all)	7	2	
Hypoalbuminaemia			
subjects affected / exposed	5 / 82 (6.10%)	2 / 82 (2.44%)	
occurrences (all)	7	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2013	This is an administrative amendment to notify that effective from November 1, 2012, Nerviano Medical Sciences S.r.l. (NMS), CRO delegated for the experimentation, conferred its business branch, including the activities carried out by its Business Unit - Department of Clinical Development "Milano International Oncology" (MIO), to the company CLIOSS Srl. Therefore, all the activities previously delegated to MIO have been transferred to CLIOSS Srl. The documents Protocol and Informed Consent have been modified with the new name of the CRO.
12 June 2015	The substantial amendment to the protocol was necessary due to the recruitment of fewer patients than expected in all the centers involved. The primary endpoint was changed: the analysis focused on disease-free survival (PFS) based on suggestions from the Regulatory Authority.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported