



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 |
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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 treat 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 treat 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 treat 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 censored 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 treated 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 treated 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 treat 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-Haenszel Chi-Square Test controlling for ECOG Performance Status | |
| Comparison groups | All patient treated with Docetaxel + Oxaliplatin +Capecitabine v All patient treat 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 treatate 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 treatate 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 occurrences (all) | 18 / 82 (21.95%) 37 | 33 / 82 (40.24%) 79 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 3 / 82 (3.66%) 6 | 10 / 82 (12.20%) 19 | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 39 / 82 (47.56%) 116 | 29 / 82 (35.37%) 71 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 18 / 82 (21.95%) 39 | 6 / 82 (7.32%) 9 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 5 / 82 (6.10%) 8 | 3 / 82 (3.66%) 3 | |
| Pyrexia subjects affected / exposed occurrences (all) | 11 / 82 (13.41%) 16 | 9 / 82 (10.98%) 10 | |
| Eye disorders | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 8 / 82 (9.76%) 14 | 0 / 82 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 18 / 82 (21.95%) 31 | 17 / 82 (20.73%) 35 | |
| Constipation subjects affected / exposed occurrences (all) | 14 / 82 (17.07%) 23 | 13 / 82 (15.85%) 20 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 38 / 82 (46.34%) 76 | 24 / 82 (29.27%) 37 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 5 / 82 (6.10%) 6 | 2 / 82 (2.44%) 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 | <p>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.</p> <p>The documents Protocol and Informed Consent have been modified with the new name of the CRO.</p> |
| 12 June 2015 | <p>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.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported