Clinical trial results:
Ensayo clínico fase II aleatorizado de vinorelbina oral y cisplatino como tratamiento de inducción y después con radioterapia concomitante frente a cisplatino y etopósido con radioterapia concomitante en cáncer de pulmón no microcítico localmente avanzado irresecable.

Phase II randomized clinical trial of oral vinorelbine and cisplatin as induction treatment and then with concomitant radiotherapy versus to cisplatin and etoposide with concomitant radiotherapy in Locally advanced unresectable non-small cell lung cancer.

Summary

EudraCT number	2010-022927-31
Trial protocol	ES
Global end of trial date	16 April 2017
Results information	
Result version number	v1 (current)
This version publication date	02 September 2020
First version publication date	02 September 2020
Summary attachment (see zip file)	GECP_RENO_final report_summary (CSR_Informe clínico ICH_RENO_v.1.0 final. 30Jun2020_resumen.pdf)

Trial information

Trial identification	
Sponsor protocol code	GECP10/02
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Grupo Español de Cáncer de Pulmón
Sponsor organisation address	Avenida Meridiana 358, 6ª planta, Barcelona, Spain, 08027
Public contact	Eva Pereira Álvarez, Grupo Español de Cáncer de Pulmón, +34 934302006, epereira@gecp.org
Scientific contact	Mariano Provencio, Grupo Español de Cáncer de Pulmón, +34 934302006, epereira@gecp.org

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	08 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2017
Global end of trial reached?	Yes
Global end of trial date	16 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

▪ To assess the efficacy (progression-free survival (PFS)) of oral vinorelbine and cisplatin as induction treatment and then with concomitant radiotherapy. PFS is defined as the time from the time of randomization to the time of progression or death from any cause without the progression of the disease studied having occurred. In other words, patients who die without evidence of progression will be considered events on the date of death and those who have not progressed at the time of the analysis will be censored with the date of the last control.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Not applicable

Evidence for comparator:

Currently, for clinically selected unresectable stage III patients with good general condition, correct lung function, no weight loss> 5%, a normal lung volume receiving> 20Gy (V20) ≤ 35%, and with the data of a recent meta-analysis, the administration of concomitant chemotherapy and radiotherapy was consider the treatment of choice.
At the moment there is no systemic treatment considered as standard nor a dose of Standard radiotherapy for these patients who are tributary to a treatment with chemotherapy and radical radiotherapy.
From the literature data it appears that the cisplatin / etoposide combination is one of the most active with a median survival of 23.2 months (overall 3-year survival of 26.1%, progression-free survival around 10 months), but with some degree of toxicity (17% grade 3-4 esophagitis and 32% grade neutropenia 3-4) .

Actual start date of recruitment	05 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 140

Worldwide total number of subjects	140
EEA total number of subjects	140

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)	115
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 22 centers in Spain.
Overall 140 patients were enrolled between August 5th, 2011 and December 16th.

Pre-assignment

Screening details:

Expected patients: n = 134
Patients included: n = 140: 69 patients in Branch A (treatment of oral Vinorelbine + Cisplatin + Radiotherapy) and 71 patients in Branch B (Etoposide + Cisplatin + Radiotherapy)
Eligible patients: n = 130
Evaluable patients: n = 126

Pre-assignment period milestones

Number of subjects started	140
Number of subjects completed	140

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	oral Vinorelbine + Cisplatin + Radiotherapy

Arm description:

Eligible participants in the OVP arm received oral vinorelbine on days 1 and 8 during four 3-week cycles with cisplatin 80 mg/m2 administered intravenously (IV) on day 1 of each cycle (see Fig. 1). Oral vinorelbine dosage was 60 mg/m2 on cycle 1, 80 mg/m2 on cycle 2 and 40 mg/m2 on cycles 3 and 4. Concomitant radiotherapy consisted on 2 Gy/day administered concomitantly along cycles 3 and 4 (66 Gy).
Patients received concurrent thoracic radiotherapy (TRT) using three-dimensional conformal radiotherapy technique (3DCRT). A total TRT dose of 66 Gy was administered according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) and the International Commission on Radiation Units & Measurements report 50 (ICRU-50)

Arm type	Experimental
Investigational medicinal product name	Oral vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral Vinorelbine: Will be administered on days 1 and 8 every 21 days for a total of 4 cycles according to the following dosage:
- Cycle 1: 60 mg / m2 day 1 and 8 of the cycle
- Cycle 2: 80 mg / m2 day 1 and 8 of the cycle
- Cycle 3 and 4 (concomitant with radiotherapy): 40 mg / m2 day 1 and 8 of each cycle
Oral vinorelbine on day 1 of the cycle will be administered 30 to 60 minutes before the infusion of cisplatin.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin: 80 mg / m2 day 1 every 21 days for 4 cycles

Arm title	Etoposide and cisplatin with radiotherapy

Arm description:

Patients received etoposide 50 mg/m2 IV on days 1–5 of two 4-week cycles and cisplatin 50 mg/m2 IV on days 1 and 8 of each cycle. Concomitant radiotherapy 2 Gy/day (66 Gy) was administered on days 1–33. Patients received concurrent thoracic radiotherapy (TRT) using three-dimensional conformal radiotherapy technique (3DCRT). A total TRT dose of 66 Gy was administered according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) and the International Commission on Radiation Units & Measurements report 50 (ICRU-50)

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

Dosage and administration details:

Patients received etoposide 50 mg/m2 IV on days 1–5 of two 4-week cycles

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

Dosage and administration details:

Patients received cisplatin 50 mg/m2 IV on days 1 and 8 of each cycle (of two 4-week cycles)

Number of subjects in period 1	oral Vinorelbine + Cisplatin + Radiotherapy	Etoposide and cisplatin with radiotherapy
Started	69	71
Completed	64	66
Not completed	5	5
Protocol deviation	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	140	140	
Age categorical Units: Subjects			
Adults (18-64 years)	105	105	
From 65-84 years	35	35	
Age continuous Units: years			
median	62		
full range (min-max)	39 to 76	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	121	121	
Smoking status Units: Subjects			
Never	2	2	
Former	64	64	
Smoker	74	74	
ECOG Status Units: Subjects			
ECOG 0	63	63	
ECOG 1	77	77	
Histopathology Units: Subjects			
Squamous cell /epidermoid carcinoma	69	69	
Adenocarcinoma	63	63	
Large cell carcinoma	5	5	
Other	3	3	
Initial Stage Units: Subjects			
IA stage	1	1	
IIIA stage	62	62	
IIIB stage	74	74	
IV stage	3	3	
Treatment compliance Units: Subjects			
C1	8	8	
C2	68	68	
C3	1	1	
C4	57	57	
No treated	6	6	

Subject analysis sets	
Subject analysis set title	Etoposide + Cisplatin + Radiotherapy
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT group with Etoposide + Cisplatin + Radiotherapy treatment	
Subject analysis set title	Vinorelbine + Cisplatin + Radiotherapy
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT population with Vinorelbine + Cisplatin + Radiotherapy treatment	

Reporting group values	Etoposide + Cisplatin + Radiotherapy	Vinorelbine + Cisplatin + Radiotherapy	
Number of subjects	71	69	
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous Units: years			
median	61,3	63,6	
full range (min-max)	43 to 76	39 to 75	
Gender categorical Units: Subjects			
Female	61	60	
Male	10	9	
Smoking status Units: Subjects			
Never	0	2	
Former	28	36	
Smoker	43	31	
ECOG Status Units: Subjects			
ECOG 0	30	33	
ECOG 1	41	36	
Histopathology Units: Subjects			
Squamous cell /epidermoid carcinoma	35	34	
Adenocarcinoma	33	30	
Large cell carcinoma	2	3	
Other	1	2	
Initial Stage Units: Subjects			
IA stage	1	0	
IIIA stage	30	32	
IIIB stage	39	35	
IV stage	1	2	

Treatment compliance Units: Subjects			
C1	5	3	
C2	63	5	
C3	0	1	
C4	0	57	
No treated	3	3	

End points

End points reporting groups

Reporting group title	oral Vinorelbine + Cisplatin + Radiotherapy

Reporting group description:

Eligible participants in the OVP arm received oral vinorelbine on days 1 and 8 during four 3-week cycles with cisplatin 80 mg/m2 administered intravenously (IV) on day 1 of each cycle (see Fig. 1). Oral vinorelbine dosage was 60 mg/m2 on cycle 1, 80 mg/m2 on cycle 2 and 40 mg/m2 on cycles 3 and 4. Concomitant radiotherapy consisted on 2 Gy/day administered concomitantly along cycles 3 and 4 (66 Gy).
Patients received concurrent thoracic radiotherapy (TRT) using three-dimensional conformal radiotherapy technique (3DCRT). A total TRT dose of 66 Gy was administered according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) and the International Commission on Radiation Units & Measurements report 50 (ICRU-50)

Reporting group title	Etoposide and cisplatin with radiotherapy

Reporting group description:

Patients received etoposide 50 mg/m2 IV on days 1–5 of two 4-week cycles and cisplatin 50 mg/m2 IV on days 1 and 8 of each cycle. Concomitant radiotherapy 2 Gy/day (66 Gy) was administered on days 1–33. Patients received concurrent thoracic radiotherapy (TRT) using three-dimensional conformal radiotherapy technique (3DCRT). A total TRT dose of 66 Gy was administered according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) and the International Commission on Radiation Units & Measurements report 50 (ICRU-50)

Subject analysis set title	Etoposide + Cisplatin + Radiotherapy
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT group with Etoposide + Cisplatin + Radiotherapy treatment

Subject analysis set title	Vinorelbine + Cisplatin + Radiotherapy
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT population with Vinorelbine + Cisplatin + Radiotherapy treatment

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

To evaluate the efficacy (progression-free survival, PFS) of oral vinorelbine and cisplatin as induction treatment and then with concomitant radiotherapy. PFS is defined as the time from the time of randomization to the time of progression or death from any cause without the progression of the disease studied having occurred. In other words, patients who die without evidence of progression will be considered events on the date of death and those who have not progressed at the time of the analysis will be censored with the date of the last control.

End point type	Primary

End point timeframe:

At the end of study

End point values	oral Vinorelbine + Cisplatin + Radiotherapy	Etoposide and cisplatin with radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: Months				
median (confidence interval 95%)	10.8 (7.4 to 14)	9.1 (5.5 to 12.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The median progression-free survival was 10.8 months (95% CI: 7.5-14) in the group VC patient group and 9.1 months (95% CI: 5.5-12.7) in the group EC patients with no statistically significant differences (p = 0.389).
According to the main objective of the study in evaluating the efficacy of oral vinorelbine and cisplatin as induction treatment and then with concomitant radiotherapy, was considered a positive study, if the median PFS was higher 12.58 months. Therefore, the study is negative

Comparison groups	oral Vinorelbine + Cisplatin + Radiotherapy v Etoposide and cisplatin with radiotherapy
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.389 [2]
Method	Kaplan-Meier
Parameter estimate	Mean difference (final values)
Point estimate	12.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.5
upper limit	14

Notes:

[1] - According to the main objective of the study in evaluating the efficacy (survival free of progression, SLP) of oral vinorelbine and cisplatin as induction treatment and then with concomitant radiotherapy, was considered a positive study, if the median PFS was higher 12.58 months. Therefore, given that the median obtained at this time is 10.8 months, we consider the study to be negative.
[2] - Median PFS was 10.8 months (CI95%7.7-13.8) in the OVP arm and 9.6 months in the EP arm (CI95%4.4-14.8). Comparison of median PFS between arms was statistically non-significant (p = 0.389)

Secondary: Overall survival

End point title	Overall survival

End point description:

The overall survival was analyzed as the time between the randomization of the treatment and the death from any cause. Live patients were censored on the date of the last control of follow up.

End point type	Secondary

End point timeframe:

At the end of study

End point values	oral Vinorelbine + Cisplatin + Radiotherapy	Etoposide and cisplatin with radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: Months				
median (confidence interval 95%)	38 (21.4 to 54.7)	29.5 (22.3 to 36.7)		

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The overall survival was analyzed as the time between the randomization of the treatment and the death from any cause.

Comparison groups	Etoposide and cisplatin with radiotherapy v oral Vinorelbine + Cisplatin + Radiotherapy
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.65 [4]
Method	Kaplan-Meier
Parameter estimate	Mean difference (final values)
Point estimate	38
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.4
upper limit	54.7

Notes:

[3] - The median overall survival was 38 months (95% CI: 21.4-54.7) in patients in the Experimental Branch: Oral Vinoreline+ Cisplatine and 29.5 months (22.3-36.7) in patients of Comparator Branch: Etoposide and Cisplatine without finding differences statistically significant (p = 0.65) as shown by the Kaplan Meier curve.

[4] - Comparison of the overall survival was non-significantly different between experimental and comparator branch.

Secondary: Response duration

End point title	Response duration

End point description:

Describe and compare the duration of the response of the two branches, determined from the date in that the tumor response is objectified until the progression appears.

End point type	Secondary

End point timeframe:

At the end of study

End point values	oral Vinorelbine + Cisplatin + Radiotherapy	Etoposide and cisplatin with radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: Month				
median (confidence interval 95%)	11.9 (6.84 to 16.96)	9.1 (2.61 to 15.59)		

Statistical analyses

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Compare the duration of the response of the two branches, determined from the date in that the tumor response is objectified until the progression appears.

Comparison groups	oral Vinorelbine + Cisplatin + Radiotherapy v Etoposide and cisplatin with radiotherapy
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.373 [6]
Method	Kaplan-Meier
Parameter estimate	Median difference (final values)
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.61
upper limit	16.96

Notes:

[5] - The duration of response was analyzed in the treatment group of Experimental Branch and in the group Comparator Branch treatment without statistically significant differences between the treatment groups (p = 0.373)
[6] - Comparison of the duration of the response was non-significantly different.

Secondary: Comparison of objective tumor response by treatment branch

End point title	Comparison of objective tumor response by treatment branch

End point description:

Describe and compare the objective response rate of the two treatment branches, by evaluating of the target lesions according to the RECIST criteria (version 1.1).

End point type	Secondary

End point timeframe:

At the end of study

End point values	oral Vinorelbine + Cisplatin + Radiotherapy	Etoposide and cisplatin with radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: Subjects				
Objetive Response YES	39	41		
Objetive response NO	24	22		

Statistical analyses

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Describe and compare the objective response rate of the two treatment branches, by evaluating of the target lesions according to the RECIST criteria (version 1.1).

Comparison groups	oral Vinorelbine + Cisplatin + Radiotherapy v Etoposide and cisplatin with radiotherapy
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.711
Method	Kaplan-Meier

Notes:

[7] - The objective response by treatment branch was compared and no statistically significant differences were found (p = 0.711).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event or breakdown occurring during the course of the study.

Adverse event reporting additional description:

The severity of AE will be determined using CTCAE version 4.0.
In the OVP arm, treatment discontinuation due to death was reported in three cases (one due to disease progression, one to non-treatment-related (NTR) bronchopulmonary haemorrhage and one to cisplatin-related nephrotoxicity). In EC arm one death was due G4 necrotizing fasciitis (NTR).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	oral Vinorelbine + Cisplatin + Radiotherapy

Reporting group description:

Eligible participants in the OVP arm received oral vinorelbine on days 1 and 8 during four 3-week cycles with cisplatin 80 mg/m2 administered intravenously (IV) on day 1 of each cycle (see Fig. 1). Oral vinorelbine dosage was 60 mg/m2 on cycle 1, 80 mg/m2 on cycle 2 and 40 mg/m2 on cycles 3 and 4. Concomitant radiotherapy consisted on 2 Gy/day administered concomitantly along cycles 3 and 4 (66 Gy).
Patients received concurrent thoracic radiotherapy (TRT) using three-dimensional conformal radiotherapy technique (3DCRT). A total TRT dose of 66 Gy was administered according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) and the International Commission on Radiation Units & Measurements report 50 (ICRU-50)

Reporting group title	Etoposide and cisplatin with radiotherapy

Reporting group description:

Patients received etoposide 50 mg/m2 IV on days 1–5 of two 4-week cycles and cisplatin 50 mg/m2 IV on days 1 and 8 of each cycle. Concomitant radiotherapy 2 Gy/day (66 Gy) was administered on days 1–33. Patients received concurrent thoracic radiotherapy (TRT) using three-dimensional conformal radiotherapy technique (3DCRT). A total TRT dose of 66 Gy was administered according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) and the International Commission on Radiation Units & Measurements report 50 (ICRU-50)

Serious adverse events	oral Vinorelbine + Cisplatin + Radiotherapy	Etoposide and cisplatin with radiotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 66 (24.24%)	18 / 68 (26.47%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	2	1	
Injury, poisoning and procedural complications			
Vertebral fracture			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Superior vena cava syndrome			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Vasovagal syncope			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 66 (7.58%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 66 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			
subjects affected / exposed	0 / 66 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 66 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Mucositis			

subjects affected / exposed	1 / 66 (1.52%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal stricture			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomits			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagitis			
subjects affected / exposed	0 / 66 (0.00%)	4 / 68 (5.88%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 66 (3.03%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Broncopulmonar hemorragia & necrosis			

subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory infection			
subjects affected / exposed	0 / 66 (0.00%)	4 / 68 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrological toxicity			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infections and infestations			
Necrotizing fasciitis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	oral Vinorelbine + Cisplatin + Radiotherapy	Etoposide and cisplatin with radiotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 66 (21.21%)	43 / 68 (63.24%)	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Aphonia			
subjects affected / exposed	3 / 66 (4.55%)	0 / 68 (0.00%)	
occurrences (all)	3	0	
Seizure crisis			
subjects affected / exposed	0 / 66 (0.00%)	3 / 68 (4.41%)	
occurrences (all)	0	3	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	6 / 66 (9.09%)	1 / 68 (1.47%)	
occurrences (all)	6	1	
Chest pain			
subjects affected / exposed	1 / 66 (1.52%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Anorexy			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Lipothymia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 66 (1.52%)	4 / 68 (5.88%)	
occurrences (all)	1	4	
Neutropenia			
subjects affected / exposed	10 / 66 (15.15%)	19 / 68 (27.94%)	
occurrences (all)	10	19	
Hemoglobin	Additional description: Hematologic toxicity		
subjects affected / exposed	1 / 66 (1.52%)	4 / 68 (5.88%)	
occurrences (all)	1	4	
Leukocytes	Additional description: Hematologic toxicity		
subjects affected / exposed	5 / 66 (7.58%)	12 / 68 (17.65%)	
occurrences (all)	5	12	
Neutrophils	Additional description: Hematologic toxicity		
subjects affected / exposed	11 / 66 (16.67%)	12 / 68 (17.65%)	
occurrences (all)	11	12	
Platelets	Additional description: Hematological toxicity		
subjects affected / exposed	3 / 66 (4.55%)	4 / 68 (5.88%)	
occurrences (all)	3	4	
INR increase			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	

Lymphopenia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	3 / 66 (4.55%)	2 / 68 (2.94%)	
occurrences (all)	3	2	
Esophagitis			
subjects affected / exposed	1 / 66 (1.52%)	12 / 68 (17.65%)	
occurrences (all)	1	12	
Mucositis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Vomits			
subjects affected / exposed	4 / 66 (6.06%)	1 / 68 (1.47%)	
occurrences (all)	4	1	
Esophageal stricture			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Diverticulitis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Odynophagia			
subjects affected / exposed	0 / 66 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 66 (3.03%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Respiratory infection			
subjects affected / exposed	2 / 66 (3.03%)	3 / 68 (4.41%)	
occurrences (all)	2	3	
Bronchospasm			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Hemoptysis			

subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2	0 / 68 (0.00%) 0	
Infections and infestations Sepsis subjects affected / exposed occurrences (all)	 0 / 66 (0.00%) 0	 3 / 68 (4.41%) 3	
Metabolism and nutrition disorders Hyperglycemia subjects affected / exposed occurrences (all)	 3 / 66 (4.55%) 3	 0 / 68 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2012	Extension of the selection period that precedes registration and includes the 42-day period for completion of the valuation scans instead of 28 days. Therefore there is a period extension for the completion of the PET-CT and thoraco-abdominal CT prior to treatment period.
26 June 2013	Selection criteria are modified. It is added as new exclusion criterion: patients who have received previous surgery for the disease.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31446990