Clinical trial results:
Phase II clinical trial with tri-weekly metronomic oral vinorelbine and cisplatin as induction treatment for and subsequent concomitant with radiotherapy (RT) in patients with non small cell lung cancer (NSCLC) locally advanced unresectable.

Summary

EudraCT number	2015-003312-21
Trial protocol	ES
Global end of trial date	20 December 2019

Results information

Result version number	v1 (current)
This version publication date	03 February 2021
First version publication date	03 February 2021
Summary attachment (see zip file)	GECP_NORA_final report_summary (GECP15-02-NORA_final report summary_12Jan2021.pdf)

Trial information

Trial identification

Sponsor protocol code	GECP15/02_NORA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02709720
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	19 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2019
Global end of trial reached?	Yes
Global end of trial date	20 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy in terms of progression-free survival (PFS) of oral metronomic vinorelbine and cisplatin as an induction treatment and posteriorly with concomitant radiotherapy.

The PFS is defined as the time since the randomization until the progression documentation or exitus for any reason (any death with or without evidence of progression, will be considered events on the exitus date and these that will not progress in the moment 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: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2016
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: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

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)	45

From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initially, 68 patients were recruited in 18 centers between April 2016 and June 2017. Although one of them was excluded after not meeting the first inclusion criteria, another for not being able to start treatment and another because their treatment did not follow the protocol. Finally 65 patients were finally selected for final analysis

Pre-assignment

Screening details:

The study selected patients diagnosed with locally advanced NSCLC who had not performed no prior cytostatic, radiotherapy or surgical treatment for the disease.

Period 1

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

Arms

Arm title	Arm of study

Arm description:

2 cycles of metronomic Vinorelbine 50 mg + cisplatin 80mg/m2, followed by 2 cycles of Vinorelbine 30 mg + cisplatin 80mg/m2 concomitant with radiotherapy

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

Dosage and administration details:

Induction chemotherapy:
Metronomic oral vinorelbine: 50mg / day, on Monday, Wednesday and Friday of each week, for 2 cycles.
1 cycle equals 21 days (9 administrations of oral vinorelbine).

Concomitant chemotherapy with radiation therapy:

Metronomic oral vinorelbine: 30mg / day, on Monday, Wednesday and Friday of each week, for 2 cycles.
1 cycle equals 21 days (9 administrations of oral vinorelbine).

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

Dosage and administration details:

Induction chemotherapy:
Cisplatin: 80 mg / m2 day 1 every 21 days, for 2 cycles.
1 cycle equals 21 days (1 administration of cisplatin).

Concomitant chemotherapy with radiation therapy:
Cisplatin: 80 mg / m2 day 1 every 21 days, for 2 cycles.
1 cycle equals 21 days (1 administration of cisplatin).

Number of subjects in period 1	Arm of study
Started	65
Completed	65

Baseline characteristics

Reporting groups	
Reporting group title	Overall study (overall period)

Reporting group description: -

Reporting group values	Overall study (overall period)	Total	
Number of subjects	65	65	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
As a criterion for inclusion in the study, patients should be between 18 and 75 years old.			
Units: years			
arithmetic mean	61.9		
standard deviation	± 8.1	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	50	50	
Smoking status Units: Subjects			
Never	3	3	
Former	27	27	
Smoker	35	35	
ECOG Performance Status Units: Subjects			
ECOG 0	34	34	
ECOG 1	31	31	
First histopathological diagnosis Units: Subjects			
Squamous / epidermoid carcinoma	27	27	
Adenocarcinoma	29	29	
Large cell carcinoma	1	1	
Adenosquamous carcinoma	4	4	
Other	2	2	
Not included or provided	2	2	
Stage T Units: Subjects			

Stage TX	1	1	
Stage T1	5	5	
Stage T2	10	10	
Stage T3	13	13	
Stage T4	36	36	
Stage N Units: Subjects			
Stage N0	5	5	
Stage N1	7	7	
Stage N2	35	35	
Stage N3	18	18	
Stage M Units: Subjects			
Stage M0	65	65	
Grade Units: Subjects			
IIIA	27	27	
IIIB	38	38	
Electrocardiogram Units: Subjects			
Not done	2	2	
Normal	54	54	
Abnormal	9	9	
Respiratory function tests Units: Subjects			
Normal	64	64	
Abnormal	1	1	
Treatment compliance Units: Subjects			
C1, C2, C3 and C4 complete	51	51	
C1, C2 and C3 complete	2	2	
C1, C2 complete and C3 incomplete	1	1	
C1 and C2 complete	6	6	
C1 complete and C2 incomplete	1	1	
C1 complete	2	2	
C1 incomplete	2	2	

End points

End points reporting groups

Reporting group title	Arm of study

Reporting group description:

2 cycles of metronomic Vinorelbine 50 mg + cisplatin 80mg/m2, followed by 2 cycles of Vinorelbine 30 mg + cisplatin 80mg/m2 concomitant with radiotherapy

Primary: Progression-free Survival

End point title	Progression-free Survival[1]

End point description:

To assess the efficacy in terms of progression-free survival (PFS) of oral metronomic vinorelbine and cisplatin as induction therapy and then with concomitant radiotherapy. PFS is defined as the time from the moment of inclusion of the patient to documentation of progression or death from any cause (that is, patients who die without evidence of progression will be considered events on the date of death and those that 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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The estimated median progression-free survival (PFS) was 11.5 months (95% CI 9.6-15.4), with an estimated PFS of 79.6% (95% CI 67.5-87.6%) at 6 months, 47.8% (95% CI 35.1-59.4%) at 12 months and 25.5% (15.5-36.6%) at 24 months.
The NORA study provides a new concept to explore with the use of metronomic chemotherapy. The studied treatment achieves an estimated median PFS of 11.5 m and 47.8% (95% CI 35.1-59.4%) at 12 months, which in the case of the PACIFIC study is 16.8 m and 55 per year resp.

End point values	Arm of study			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Month				
median (full range (min-max))	11.5 (9.6 to 15.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was measured from the date of inclusion of the patient until death or loss to follow-up. In patients who have not died, the duration of survival will be censored on the date of the last contact if the patient causes loss to follow-up or on the date of the latest news.

Survival curves for overall survival have been estimated using the Kaplan-Meier method, obtaining estimates for the measures and survival rates at different times with their corresponding confidence intervals with a confidence level of 95%, using the adequate procedures for estimating these intervals.

We have an estimated median overall survival of 35.6 months (95% CI 24.4-46.8 months), with an estimated survival of 93.7% at 6 months (95% CI 84.1-97.6%) , 81.0% at 12 months (95% CI 69.0-88.7%) and 60.4% at 24 months (95% CI 47.2-71.2%).

End point type	Secondary

End point timeframe:

At the end of study

End point values	Arm of study			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Months				
median (full range (min-max))	35.6 (24.4 to 46.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response

End point title	Objective tumor response

End point description:

Objective response rate of the treatment, by assessing the target lesions according to the RECIST criteria (version 1.1).

Objective response analyses was estimated using the Kaplan-Meier method with a confidence level of 95%, using the appropriate procedures.

The best response to treatment of these 65 patients is described, with 4 patients (6.2%) presenting a complete response (95% CI 2.4-14.8%), 39 (60.0%) presenting a partial response (95% CI 47.9-71.0%), 12 (18.5%) with stable disease (95% CI 10.9-29.6%), 7 with progression (10.8%) (95% CI 5.3 -20.6%) and 3 in which the response could not be evaluated (4.6%) (95% CI 1.6-12.7%). We can see that, of the 51 patients who have completed treatment, 4 (7.8%) present a CR, 36 (70.6%) a PD and 11 (21,6%) SD. We also have 14 patients who have not completed treatment, of which 3 (21.4%) presented partial response, 1 (7.1%) stable disease, 7 (50.0%) progression and 3 (21.4%) not evaluable.

End point type	Secondary

End point timeframe:

At the end of study

End point values	Arm of study			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Subjects				
Complete response	4			
Partial response	39			
Stable disease	12			

Progression disease	7			
Not applicable / Not evaluable	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

The investigator will have to collect all adverse events once they have signed informed consent, during treatment and 30 days after the last
administration of the study.

Adverse event reporting additional description:

The severity of AE will be determined using CTCAE version 4.0.
Consistent with EudraCT disclosure specifications, GECP has reported under the SAE field "number of deaths resulting from AE" 0 deaths, because there are not deemed to be causally related to treatment by the investigator. In total were 9 exitus.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Subjects per protocol

Reporting group description: -

Serious adverse events	Subjects per protocol		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 65 (9.23%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain metastasis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Esophagitis			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal pain			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney failure			
subjects affected / exposed	3 / 65 (4.62%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Subjects per protocol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 65 (90.77%)		
Investigations			

Creatinine increased subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3		
Neutrophil count decreased subjects affected / exposed occurrences (all)	26 / 65 (40.00%) 30		
Platelet count decreased subjects affected / exposed occurrences (all)	11 / 65 (16.92%) 12		
White blood cell decreased subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2		
Dysgeusia subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3		
Headache subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2		
Paresthesia subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	32 / 65 (49.23%) 32		
General disorders and administration site conditions Edema limbs subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2		
Fatigue subjects affected / exposed occurrences (all)	26 / 65 (40.00%) 26		

Fever			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	3 / 65 (4.62%)		
occurrences (all)	3		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 65 (15.38%)		
occurrences (all)	10		
Diarrhea			
subjects affected / exposed	22 / 65 (33.85%)		
occurrences (all)	22		
Dysphagia			
subjects affected / exposed	16 / 65 (24.62%)		
occurrences (all)	16		
Esophagitis			
subjects affected / exposed	21 / 65 (32.31%)		
occurrences (all)	21		
Gastritis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences (all)	1		
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	2		
Mucositis oral			
subjects affected / exposed	7 / 65 (10.77%)		
occurrences (all)	7		
Vomiting			
subjects affected / exposed	19 / 65 (29.23%)		
occurrences (all)	19		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences (all)	1		

Dyspnoea subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3		
Hiccups subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1		
Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1		
Renal and urinary disorders Urinary tract pain subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3		
Myalgia subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	11 / 65 (16.92%) 11		
Hiperglycemia			

subjects affected / exposed	1 / 65 (1.54%)		
occurrences (all)	1		
Hypocalcemia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences (all)	1		
Hypomagnesemia			
subjects affected / exposed	3 / 65 (4.62%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 February 2017	Correct the total number of patients and sites in the study after the statistical review of the analysis initially proposed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable.

Notes: