Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Official Title: 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.

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NORA STUDY

GECP CODE15/02

Sponsor: Grupo Español de Cáncer de Pulmón

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Clinical Trial Protocol

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.

Study code: GECP 15/02

EudraCT Number: 2015-003312-21

Sponsor:

Grupo Español de Cáncer de Pulmón
Av. Meridiana, 358 6ª pl.
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Version nº 3 date 05 January 2017

SUMMARY OF STUDY

SPONSOR:	**GRUPO ESPAÑOL DE CÁNCER DE PULMÓN (GECP)**
NAME OF THE ACTIVE SUBSTANCE(S):	Cisplatine, vinorelbina oral.
Title	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
Code	GECP 15/02
Sites	18 sites in Spain
Justification	Currently, the administration of concomitant chemotherapy and radiotherapy is considered a treatment of choice for clinically selected patients with unresectable stage III tumor. There is currently no systemic treatment considered standard in combination with radical radiotherapy. Neither has a standard radiotherapy dose been established, but it is known that it should never be less than 60Gy57. Vinorelbine has been shown to have a powerful radiosensitizing effect in-vitro37. In the phase II study by Krzakowski et al., the combination of cisplatin with oral vinorelbine as induction treatment and then concomitant radiotherapy (66Gy) has provided highly encouraging efficacy results. The VORTICE study recently tested the scheme of cisplatin with oral vinorelbine maintained concomitantly with radiotherapy from the second cycle of chemotherapy. They observed a 77.3% response rate, a PFS of 12 months, and an OS of 27.8 months, but at the cost of increased toxicity primarily in the form of esophagitis. Therefore, the search for treatment schemes that improve efficacy and toxicity is a priority in this segment of the pathology. Metronomic chemotherapy was born with the idea of administering divided doses of a cytostatic, over a long period and without interruption, which could provide the advantage of exposing patients to a significant dose of chemotherapy without worsening the toxicity profile. All this makes it an attractive treatment strategy, and can also maintain a radiosensitizing effect during concomitance37,38. Given the limited experience of the combination of metronomic oral vinorelbine with cisplatin and radiotherapy in phase I41 by Krzakowski et al., the excellent tolerance of the 30mg oral vinorelbine dose on days 1, 3 and 5 with radiotherapy of the same study and the results of efficacy obtained in the phase II study42 by Lerouge et al., in the present study the efficacy of 2 induction cycles with metronomic oral vinorelbine at a dose of 50 mg on days 1, 3 and 5 will be evaluated in patients with unresectable locally advanced NSCLC of the week combined with cisplatin 80mg/m2 every three weeks, and 2 concomitant cycles of radiotherapy (66 Gy) with vinorelbine dose reduction to 30mg on days 1, 3 and 5 of each week
Study period	From the 1st quarter of 2016 to the 1st quarter of 2018, or until the inclusion of the last patient necessary to reach the sample established in the protocol of 68 patients, with a maximum follow-up of 24 months.
Objetive	**Principal Objective:** • To assess the efficacy in terms of progression-free survival (PFS) of metronomic oral vinorelbine and cisplatin as induction treatment and then with concomitant radiotherapy. PFS is defined as the time from the time of patient enrollment to documentation of progression or death from any cause (i.e., 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 either, will be censored with the date of the last control). **Secundary objective:** • Describe the objective response rate to treatment. • Describe the disease control rate. • Describe the duration of the response. • Describe the duration of disease control. • Describe the overall survival (OS) of treatment.

	• Describe the safety of the treatment. • Describe the rate of adherence to oral treatment. • Analysis of biomarkers.
Metodology	Phase II, open, multicenter, national clinical trial.
Number of patients	The required sample size is 62 evaluable patients. This figure will increase by 10% due to the possible loss of evaluable patients. Therefore, the total sample to be recruited will be 68 patients.
Diagnosis and main selection criteria	**Inclusion criteria** • Patients with histologically confirmed recent non small cell lung cancer unresectable stage IIIA and IIIB. • Perform a baseline positron emission tomography (PET-CT) to rule out the presence of distant disease and confirm that it is a non-NSCLC radical surgical treatment candidate. • The positive mediastinal lymph nodes by PET-CT must be confirmed histologically. Mediastinal involvement may be considered without histologically observe when there is a mass of lymph nodes where the margins are not distinguished. • At least one measurable lesion on computerized tomography (CT). • Performance status 0-1. • Life expectancy> 12 weeks. • Age ≥18 years and ≤ 75 years. • Right renal function: creatinine ≤ 1.5 mg / dl or creatinine clearance> 60 ml / min. • Right hematologic function: hemoglobin> 10 g / dl, neutrophils ≥ 1500 / mm3 and platelets ≥ 100,000 / mm3. • Right hepatic function: bilirubin ≤ 1.5 times the upper limit of each center, transaminases ≤ 2.5 above the normal limit. • Right lung function without bronchodilators: defined by a forced expiratory volume in 1 second (FEV1)> 50% of predicted normal volume and lung diffusing capacity for carbon monoxide (DLCO)> 40% of predicted normal. • The proportion of normal lung exposed to> 20 Gy RT (V20) shall be ≤ 35%. This must be fulfilled before the start of treatment cycle 3. • Signature of informed consent. **Exclusion criteria** • Weight loss> 10% in the 3 months prior to study entry. • Intestinal problems that do not ensure proper absorption of oral vinorelbine. • Pregnant or lactating women. Women of childbearing potential should have a negative pregnancy test, and both men and women under this condition should take contraceptive measures throughout the study. • symptomatic sensory neuropathy> grade 1 toxicity criteria according to the CTCAE v4. • Comorbidities uncontrolled. • syndrome of the superior vena cava. • pleural or pericardial effusion: are both considered as indicative of metastatic disease unless proven otherwise. Those who still remain cytologically negative for malignancy, are exudates also be excluded. It may include those with pleural effusion visible on chest radiography or too small to perform diagnostic puncture safely. • Known hypersensitivity to drugs with similar study drug structure. • Previous treatment with anticancer drugs, previous surgery or thoracic radiotherapy for lung cancer or for other reasons. • History of other malignancy treated properly within 5 years except carcinoma in situ of the cervix or breast skin and basal cell carcinoma. • Concomitant treatment with other antineoplastic drug or investigational. • Patients at any psychological, family, sociological or geographical that may hinder compliance with the study protocol and monitoring program.

	• history of neurological or psychiatric disorders that impede a properly understanding of the informed consent.
Investigational product, dose and method of administration	Cisplatin (CDDP) 10, 25 and 50 mg vials for infusion (1mg/ml), 20 mg and 30 mg oral Vinorelbine soft capsules. **Induction chemotherapy:** - Cisplatin: 80 mg/m2 day 1 every 21 days, for 2 cycles. 1 cycle equals 21 days (1 administration of cisplatin) - Metronomic oral vinorelbine: 50mg/day, on Monday, Wednesday and Friday of each week, for 2 cycles. 1 cycle is equivalent to 21 days (9 administrations of oral vinorelbine). **Concomitant chemotherapy with radiotherapy:** - Cisplatin: 80 mg/m2 day 1 every 21 days, for 2 cycles. 1 cycle equals 21 days (1 administration of cisplatin) - Metronomic oral vinorelbine: 30mg/day, on Monday, Wednesday and Friday of each week, for 2 cycles. 1 cycle is equivalent to 21 days (9 administrations of oral vinorelbine). **Radiation therapy treatment:** Prior to enrolling any patient in this study, the radiation oncologist will assess CT volumetry to ensure that treatment volumes are not likely to significantly exceed established normal tissue irradiation limits. Patients will receive concomitant chest radiotherapy (RTT), using a standard three-dimensional conformal radiotherapy (3DCRT) technique, using a linear accelerator operating with beam energy ≥ 6 MV. The total target RTT dose will be 66 Gy in 33 2 Gy daily fractions, which will be prescribed in accordance with the International Commission for Radiological Units and Measurements (ICRU) reference document ICRU 50, and administered in accordance with the recommendations of the radiotherapy group of the European Organization for Research and Treatment of Cancer (EORTC) (Senan et al., 2004) and ICRU-50 (ICRU Report 50, 1993).
Treatment duration	The expected total duration of treatment is 12 weeks, unless the patient refuses to continue, suffers from unacceptable toxicity, evidence of disease progression, or medical decision.
Evaluation criteria	**Efficacy Assessment:** Tumor assessment will be performed according to RECIST guidelines (version 1.1). The evaluation of measurable lesions will be carried out at baseline, 6 weeks after the start of induction and 4-8 weeks after the end of treatment (according to the usual practice of the center). Patients discontinuing protocol treatment for reasons other than disease progression will undergo tumor evaluations every 12 weeks until progression. Each and every one of the lesions identified and described in the baseline evaluation must be evaluated in each tumor assessment. **Safety assessment:** Safety will be assessed by: • Physical exam including functional status. • Complete blood count + platelet count. • Serum biochemistry. • Reporting of adverse events using the CTCAE classification (version 4.0).
Statistical method	The study is designed to assess median PFS. We consider an unacceptable median PFS for the experimental treatment of 10 months (p0) and an acceptable one of 15 months (p1). With a recruitment time of 24 months and a minimum follow-up of 24 months after the inclusion of the last patient, with a type I error of 0.05 (α, one-tailed test), and with a type II error of 0.1 (β). , we found that the sample size is 62 evaluable patients. This figure will increase by 10% due to the possible loss of evaluable patients. The final sample is 68 patients.
Analysis of data	**Efficacy analysis** The primary endpoint of the efficacy analysis will be progression-free survival in the intention-to-treat population. The 95% confidence interval will be provided. • The secondary efficacy objectives that will be analyzed will be:

	• The rate of objective responses to treatment. • The disease control rate. • The duration of the response. • Duration of disease control. • Progression-free survival. • Overall survival. • The rate of adherence to oral treatment **Security analysis** The maximum degree or maximum severity of toxicity, according to the NCI-CTC guide version 4.0, will be tabulated for each MedDRA "System Organ Class" (SOC) and "Preferred Term" (PT), per cycle and per patient. All the analyzes will be carried out in both forms of collection: regardless or not of the relationship with the treatment. **Statistical methodology** Descriptive methods will be used to present all relevant data: - Continuous data will be summarized by the following items: frequency, median, range, mean, standard deviation and the corresponding standard error. - The categorical data will be represented in contingency tables with their frequencies and percentages in each modality (including the lack of data modality). The 95% confidence intervals will be calculated following the exact method. Analysis of Progression-Free Survival, duration of response, disease control rate, duration of disease control, and overall survival will be performed using the Kaplan-Meier method. 95% confidence intervals will be calculated for the median.
End of study	Completion of the study is defined as documentation of the death of the last patient or the end of the follow-up period. For the analysis of the secondary objective of OS, quarterly follow-up of the patients will be necessary for at least 24 more months from the last inclusion. The end is estimated for the first quarter of 2020.