CLINICAL STUDY REPORT

Fase II Docetaxel-Oxiplatino-Capecitabina (DOX) a dosis ajustadas en pacientes con adenocarcinoma gástrico avanzado y estado general subóptimo.

Sponsor:	Grupo de Tratamiento de los Tumores Digestivos (TTD) [Spanish Cooperative Group for the Treatment of Digestive Tumors]
Study code:	TTD-08-02
EudraCT No.:	2008-001825-32
Study phase:	II
Date of final report:	28/08/2015
Version:	Final
First patient in (date):	05/11/2008
Last patient in (date):	25-04-2012
Coordinating investigator of the study:	Dr. Fernando Rivera
Sponsor's representative:	Inmaculada Ruiz de Mena

The study was conducted in accordance with the protocol, the ethical principles based on the latest current version of the Declaration of Helsinki, ICH Guidelines on Good Clinical Practice and applicable national and/or international legislation.

1. SUMMARY

Name of Sponsor/company: TTD	**INDIVIDUAL SUMMARY TABLE** Volume: Page: **Code No.:** EudraCT Nº. 2008-001825-32	(For the health authorities only)
Name of medicinal product: MiniDOX		
Name of the active substances: Docetaxel, oxaliplatin, and capecitabine		

Trial title: Fase II Docetaxel-Oxiplatino-Capecitabina (DOX) a dosis ajustadas en pacientes con adenocarcinoma gástrico avanzado y estado general subóptimo.

Investigators:

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Publication (reference):

F. Rivera, B. Massutí, M. Salcedo, J. Sastre, J. Martínez Galán, M. Valladares-Ayerbes, R. Serrano, Mª L. García de Paredes, J.L. Manzano, M. Galán, M. Alsina, A. L. Yuste Izquierdo, C. López, E. Díaz-Rubio, V. Conde, M. Reboredo, Mª T. Cano, V. Pachón, E. Aranda, Phase II trial of minidox (reduced dose Docetaxel-Oxaliplatin- Capecitabine) in "suboptimal" patients with advanced gastric cancer (AGC). TTD 08-02. *Cancer Chemother Pharmacol. 2015 Feb;75(2):319-24.*

Study period (years): 2008-2012	**Study phase:** Phase II clinical trial

Objectives:

Primary objective:

- Objective Response Rate (according to the RECIST criteria: Complete or Partial Response)

Secondary objectives:

- Disease Control Rate (Complete Response, Partial Response or Stabilization)
- DOX toxicity
- Administered dose intensity
- Progression-free survival
- Overall survival.

Methodology:
Phase II, open-label, multi-centre, prospective study. Not randomized.

Patients with anatomopathological diagnosis of gastric cancer, unresectable locally advanced, metastatic or relapsed.

With suboptimal or intermediate general state defined as: patients with ECOG 2, weight loss of 10-25% or age ≥70 years, and no significant comorbidities, functional dependence or geriatric syndromes.

Each patient received the study treatment until progression, unacceptable toxicity or voluntary abandonment were observed. In case of response or stabilization, the maximum number of administered DOX cycles was 6. Subsequently, only Capecitabine was maintained at the same dose that had been administered.

A total of 43 evaluable patients were included in the study. As planned by protocol, in a first part 18 patients were included, and since more than 2 responses were reported, another 18 patients were included (second phase). Assuming a loss of 10%, the initially planned total sample was 40 patients.

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Number of patients (planned and analysed):

Nº planned: 40
Nº included: 43
Nº. treated: 42
No. Analysed: 43

Diagnosis and main inclusion criteria:

Inclusion criteria:

1. Written informed consent prior to inclusion in the study was obtained and documented in accordance with local legal requirements.
2. Patients diagnosed histologically from adenocarcinoma on the esophagogastric union or stomach (Siewert type I, II and III) locally advanced unresectable, metastatic or relapsed;
3. Measurable disease (RECIST criteria);
4. Man or woman > 18 years of age
5. At least, one of the following characteristics:
   - Patients with ECOG 2,
   - Weight loss of 10-25% or
   - Age ≥70 years
6. Life expectancy ≥12 weeks.
7. Adequate haematological function:
   - Absolute neutrophil count ≥ 1.5 x 10^9/ L.
   - Platelet count ≥ 100 x 10^9/ L.
8. Adequate coagulation: INR ≤ 1.5 or A.Prothrombin > 70%.
9. Adequate liver function:
   - Total Bilirubin ≤ 1.5 x ULN.
   - GOT (ASAT) / GPT (ALAT) ≤2,5 the ULN. In case of liver metastases ≤ 5 x ULN
   - FA ≤ 2.5 times the ULN. In case of liver metastases ≤5 x ULN and bone metastases ≤10 x ULN).
10. Adequate renal function:
    - Creatinine clearance ≥ 50 ml / min calculated according to the Cockcroft formula. (In the case that the creatinine clearance estimated by the formula was <50 ml / min, the creatinine clearance could be recalculated, using the 24 hr urine collection method and if the value is> 50 ml / min, the patient could be eligible to participate in the study).
11. Adequate oral intake.
12. Normal cardiac function, without signs or symptoms of heart failure or ischemic heart disease in the previous 6 months. Ejection fraction (EF) > 50% in case of doubts.
13. All women of childbearing age should have a serum- or urine-negative pregnancy test (minimum sensitivity of 25 IU/L of BHCG) within two weeks prior to study inclusion.
14. Patients of childbearing age had to follow an effective contraception method throughout all the treatment.
15. Patients had to be treated and studied in the participating center.
16. The patients had to be accessible for treatment and follow-up, implying the imposition of reasonable geographical limits. They should be able to adhere to the protocol throughout the duration of the study.

Exclusion criteria:

1. Non-measurable lesion as only-disease evidence.
2. Previous chemotherapy treatment for advanced disease. It was not an exclusion criterion to have received chemo- or radiotherapy for previously localized disease provided if this treatment had been completed more than 1 year before, and in the case of only measurable disease within a previously radiated area, progression of that injury has been documented before inclusion.
3. Other malignancies diagnosed in the previous five years, except spinocellular or basal cell carcinomas of the skin or in situ carcinoma of the cervix treated adequately.

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4. Known hypersensitivity to Docetaxel, Oxaliplatin or Capecitabine.
5. Evidence of metastasis in the central nervous system (CNS). Patients with a history of uncontrolled attacks or disorders of the CNS, or psychiatric disability that, in the opinion of the investigator, had clinical relevance that prevents informed consent or interferes with treatment compliance.
6. History of serious or unexpected reactions to fluoropyrimidines' treatment, and/or patients with a proven dehydropyrimidine dehydrogenase (DPD) deficiency.
7. Patients with performance status greater than 2 or with weight loss greater than 25% in the last 3 months.
8. Patients classified as delicate or "fragile" because they meet any of the following criteria:
   - Dependence on one or more daily living activities according to Katz's formal scale of activities of daily living (ADL).
   - Three or more comorbid entities by evaluating the presence of the following processes: congestive heart failure; clinically significant cardiac valvulopathy, coronary artery disease, moderate or severe chronic pulmonary disease (obstructive or restrictive), cerebrovascular disease, peripheral neuropathies, chronic renal failure, uncontrolled hypertension, uncontrolled diabetes, concomitant neoplasms (other than current gastric cancer), collagen vascular diseases, moderate-severe chronic liver disease, and disabling arthritis.
   - Presence of geriatric syndromes: moderate-severe dementia; delusions in stress situations (urinary or respiratory infection, angina or drugs); moderate-severe depression that interferes with the patient's usual activity; frequent falls (3 or more per month); inattention (Who could help you in case of emergency?); urinary incontinence in the absence of stress, infection, diuretics or prostatic hyperplasia; fecal incontinence in the absence of diarrhea or laxatives; osteoporotic fractures of long bones or vertebral crushing.
9. Presence of concomitant important cardiovascular disease considering as such the presence of any of the following:
   - History of symptomatic atrioventricular arrhythmias and/or
   - Not medically controlled congestive heart failure. In case of doubt if FE <50%, patients were excluded and/or
   - Myocardial infarction 12 months prior to recruitment and/or
   - Symptomatic ischemic heart disease and/or
   - Evidence of clinical or subclinical pulmonary thromboembolism (PTE), detected by angioCT, in the month prior to inclusion. In the case of patients with deep vein thrombosis (DVT), they could be included but it was necessary previously to rule out PTE presence by angioCT and to have, at least two weeks before the inclusion, the DVT already stabilized and treated with low molecular weight heparin at therapeutic doses.
10. Presence of active infectious process. If leukocytosis > $12x10^9$/L or fever > 38 ºC, chest X-ray, blood culture, and negative urine culture were required within 5 days prior to inclusion.
11. Serious underlying medical condition (eg, HIV, etc...) that could impair the patient's ability to receive treatment protocol.
12. Severe or poorly controlled concomitant diseases.
13. Any other condition or therapy that in the opinion of the investigator or by indication of the prospect could might present a risk to the patient or interfere with the study objectives.
14. Treatment with any other not marketed investigational drug within 30 days prior to the treatment start.

Investigational product, dose and dosing regimen, batch number:

The hydration and antiemetic guidelines were those of each center.

- Docetaxel
  Dose: 40 mg/m^2
  Administration route: 60-minute intravenous infusion
  Administration schedule: Day 1
- Oxaliplatin
  Dose: 80 mg / m2
  Administration route: 120-minute intravenous infusion
  Administration schedule: Day 1

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- Capecitabine
  Dose: 625 mg/m^2/12h
  Administration route: Oral
  Administration schedule: continued from day 1

The cycle duration was 21 days.

Oxaliplatin: Commercialized in Spain under the name Eloxatin® from Sanofi-Aventis. Pharmaceutical form: 10-ml vials of solution for infusion containing 50 mg of oxaliplatin and 20 ml of solution for infusion containing 100 mg of oxaliplatin.

Docetaxel: Commercialized in Spain under the name Taxotere® from Sanofi Aventis. Pharmaceutical form: 0.5-ml vials with 20 mg or 2-ml vials with 80 mg.

Capecitabine: Commercialized in Spain under the name Xeloda® from Roche Farma. Pharmaceutical form: 500-mg and 150-mg tablets.

Sanofi-aventis, owner of the investigational drug, supplied the investigational product free of charge: Oxaliplatin (Eloxatin®). Docetaxel (Taxotere®) and capecitabine (Xeloda®) were approved in the reference disease and are part of the usual disease treatment, not assuming any extra cost for the Hospital. The supply of said drug followed the usual pathways established in each center.

Control treatment, dose and dosing regimen, batch number

Not applicable

Treatment duration:

Each patient received the study treatment until disease progression, unacceptable toxicity or patient consent withdrawal were observed. In case of response or stabilization, the maximum number of DOX cycles to be administered was 6. Subsequently, only capecitabine was maintained at the same dose that had been administered.

Evaluation criteria:

Primary efficacy endpoint

Objective response: the objective response of the measurable disease was evaluated according to the RECIST criteria, through of diagnostic imaging studies: conventional computerized tomography (CT), helical CT, magnetic resonance imaging or chest x-ray (documentation of target and non-target lesions). The response obtained was confirmed with a new evaluation of the response done in a period of no less than 4 weeks from the date on which the response criteria was met for the first time.
tumour disease was evaluated in the baseline visit (in the previous 28 days prior to the administration of the first dose of the study treatment), and every 6 weeks during the treatment phase. The treatment response was classified as complete response (CR), partial response (PR), stable disease (SD) and disease progression (DP) according to RECIST criteria.
Response rate was defined as: Nº of CR + PR / Nº. of patients included in the study.

Secondary efficacy endpoints:

As part of the efficacy evaluation, the following secondary endpoints were also collected: disease control rate, dose intensity administered, disease-free survival, overall survival.

- Disease control rate: It was defined as: Nº of CR + DP + SD / Nº of patients included in the study
- Intensity of administered dose: The dose intensity finally administered of both Docetaxel and oxaliplatin and capecitabine was quantified.
- Progression-free survival (PFS): time elapsed from study inclusion until disease progression or death due to any cause, or until study closure at the date of the last follow-up study visit.

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- Overall survival (OS): time from study inclusion until date of death due to any cause, or until study closure at the date of the last follow-up study visit.

Safety assessments:

In order to evaluate the treatment safety, all the adverse events (AE) reported during the study (from informed consent signature until 28 days after the last administered dose of treatment) were recorded, collecting information on the maximum intensity, causal relationship with the study treatments, and AE duration and resolution. AEs were evaluated using the CTC (Common Toxicity Criteria) classification version 3.0 of the National Cancer Institute (NCI) of Canada.

Statistical methods:

Justification of the sample size calculation

The calculation of the sample size was based on the response rate (RP + RC) and on the Simon's optimal two-stage design. A minimum response rate of 10% (p0) and 30% (p1) were considered as a desirable response rate. Type I and II errors were set at 0.05 and 0.10 respectively, so if the response rate was less than 10% the probability of accepting incorrectly the treatment was less than 5%, whereas if the response rate was higher than 30%, the probability of rejecting incorrectly the hypothesis for the rest of the study was 10%. Using the parameters mentioned above, a maximum of 36 evaluable patients were required. In the first part of the study, 18 patients were included. If only two patients had response, the study was expected to end. However, since more than 3 patients responded, 18 more patients were further included (second phase). As planned by protocol, if more than 6 responses were observed among the 36 evaluable patients, the proposed treatment strategy should be considered for further development. Considering an expected 10% rate of non-evaluable patients, the final sample initially required was 40 patients.

Populations analysed

The following populations were defined for the study analyses:

- *Intention-to-treat population (ITT)*: all the patients included in the trial, even those who had not yet started the study treatment.
- *Safety population (SP)*: treated patients, that is, those who had received at least one dose of the study medication.

Statistical methods

Continuous variables were expressed by mean, median and standard deviation statistics; qualitative variables were expressed by absolute and relative frequencies.

In the descriptive analysis of qualitative variables, two columns of percentages are presented: the total percentage (% total) and the valid percentage (valid %); that is, the percentage on the sum of the valid answers plus the values without data, and the percentage over the total valid answers.

Efficacy analysis was conducted on the ITT population. The response rate was calculated with percentage frequencies, and 95% confidence intervals (CI). The PFS and OS analyses were performed using the Kaplan-Meier method, providing median, mean, 95% CI, as well as the event and number of censored events and cases.

Safety analysis was conducted on the SP. Adverse event (AE) were grouped according to categories established by CTCAE v3.0 from the original term registered by the investigator, and their frequency was estimated. AEs were grouped according to intensity, and severe AEs were described. The maximum grade was calculated for each AE collected throughout all treatment cycles of each patient.

The statistical package used for the data analysis was the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA).

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RESULTS/CONCLUSIONS SUMMARY

Baseline and demographic characteristics of the study population

A total of 43 patients (ITT) were included in the study population. One patient did not take the medication of the study therefore it was included in the ITT but not in the safety population (N = 42 patients).
Patients' characteristics were: ECOG = 2 in 12 patients, weight loss of 10-25% in 23 patients; median age of 73.3 years (40-88), 32 men; locally advanced disease in 8 patients / metastatic disease in 35 patients; primary tumour site: gastric in 32 patients and esophagogastric junction (EGJ) in 11 patients.

Six cycles of docetaxel and oxaliplatin were administered in 53% and 46% of patients, respectively, and 58% were treated with six or more cycles of capecitabine. Dose reduction of docetaxel and oxaliplatin was necessary in 45% of the patients. In 19 patients, the doses of docetaxel and oxaliplatin were increased to the level +1 and in 8 of them to the level +2. Mean relative administered dose intensity of docetaxel, oxaliplatin and capecitabine was 89%, 88% and 85%, respectively.

Efficacy results:

The confirmed overall response rate (CR + PR) was 55.8% (95% CI: 39.9-70.9%), and disease control rate (RC + RP + EE) was 83.7% (95% CI: 69.3%-93.2%). A total of 23 patients achieved PR, 1 patient achieved CR, 12 patients achieved SD, and 3 patients achieved DP. In 4 patients, the response was not evaluated. The median duration of the response was 5.3 months (95% CI: 1.3 - 9.4 months).

The median and 1-year actuarial PFS were 5.5 months (95% CI: 3.8-7.2 months) and 19% (95% CI: 7.0-30.2), respectively. The median and 1-year actuarial OS were 13.3 months (95% CI: 7.7-19.0 months) and 53.3% (95% CI: 38.6-68.4), respectively.

With a median follow-up time of 32 months, 36 patients died (toxicity: 4 patients; disease progression: 32 patients) and 7 patients were still alive with disease.

Safety results:

All patients presented at least one AE during the study. Of the total of patients, 32 (76%) had at least one AE of grade 3 or 4. The most frequent grade 3-4 AEs were: neutropenia in 7 patients (16.7%; febrile neutropenia: 3 patients), pulmonary embolism (PE) in 6 patients (14.3%; 3 of them suffered sudden death with suspected unconfirmed PE and 2 were asymptomatic), diarrhoea in 9 patients (21.4%); paronychia in 6 patients (14.3%); ictus in 1 patient (2.4%), renal failure in 1 patient (2.4%; patient suffered an infection/bacteraemia without neutropenia and died), hand-foot syndrome in 4 patients (9.5%), and asthenia in 9 patients (21.4 %).

CONCLUSIONS

We consider that, although miniDOX has shown relevant toxicity (especially PTEs), its activity is encouraging in the "suboptimal" patients with advanced gastric cancer (AGC) and this combination should be further investigated in this setting.