Clinical Study Synopsis Report

Protocol Identification No.:	TTD-06-05
MS Identification No.:	62202_765
Eudra CT No.:	2006-007062-11
Title:	Open-Label, Non-Randomized, Multicentre Phase II Study to Evaluate the Safety and Efficacy of Cetuximab (Erbitux®) in Combination with Oxaliplatin and Capecitabine (Xelox) for 12 Weeks Followed by Maintenance Therapy with Cetuximab and Capecitabine as First-Line Therapy in Elderly Patients with Metastatic Colorectal Cancer
Short Title:	NA
Development Phase:	Phase II clinical trial
Investigational Product:	Cetuximab (Erbitux®)
Drug/Dosage:	Cetuximab: initial dose of 400 mg/m^2 and then 250 mg/m^2 weekly
Treatment Duration:	12 weeks of combined therapy followed by maintenance therapy
Indication:	Elderly patients with metastatic colorectal cancer (mCCR)
Trial Design:	Open-label, non-randomized, multicentre
Trial Initiation Date:	31/10/2007
Trial Completion Date:	21/08/2008
Coordinating Investigators:	Dr. Javier Sastre and Dr. Eduardo Díaz Rubio
Sponsor:	Spanish Group for Treatment of Digestive Tumors (TTD)
Sponsor Contact:	Inma Ruiz de Mena
Date of Report:	13/09/2012

This trial was performed in compliance with Good Clinical Practice (GCP).

1 SYNOPSIS

Title of Trial: Open-Label, Non-Randomized, Multicentre Phase II Study to Evaluate the Safety and Efficacy of Cetuximab (Erbitux®) in Combination with Oxaliplatin and Capecitabine (Xelox) for 12 Weeks Followed by Maintenance Therapy with Cetuximab and Capecitabine as First-Line Therapy in Elderly Patients with Metastatic Colorectal Cancer
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Publication (reference): NA

Trial Period (years): 2007-2009	**Phase of Development:** Phase II clinical trial

Objectives:

Primary objective:

- To evaluate the confirmed objective response rate from the combination treatment of cetuximab, oxaliplatin and capecitabine for 4 cycles followed by treatment with cetuximab and capecitabine as first-line treatment in elderly patients with metastatic colorectal cancer

Secondary objectives:

- Disease control (objective responses and stabilizations)
- Safety Profile
- Time to progression and progression-free survival
- Time to treatment failure
- Determining the time to onset of response
- Duration of response
- Overall Survival
- To assess genetic and protein factors as potential predictors of treatment toxicity and response (EGFR gene amplification by FISH, repetitions number of CA sequence in intron 1, serum levels of the extracellular EGFR domain; EGFR, AKT, MAPK and PTEN expression, and EGFR, PI3KCA, K-RAS and B-RAF mutations).

Methodology:

- Open-label, non-randomized, multicentre phase II clinical trial
- All patients received 4 cycles (the expected length of each cycle was 3 weeks) with oxaliplatin, capecitabine (Xelox) and cetuximab combination treatment, followed by capecitabine and cetuximab until disease progression, onset of unacceptable drug toxicity or patient consent withdrawal.
- If a patient had unacceptable toxicity to one of the study drugs, the treatment with that drug was discontinued but the patient continued receiving the other drugs until disease progression or onset of unacceptable drug toxicity. This means that for capecitabine and/or oxaliplatin intolerance cases after initiation of study treatment, patients could continue receiving cetuximab monotherapy and/or in combination with one of two chemotherapy drugs. For cetuximab intolerance cases, patients could continue receiving capecitabine and/or oxaliplatin.
- Cetuximab treatment was not delayed for toxicity related to chemotherapy and vice versa.
- After study treatment completion patients were followed until death, in order to confirm disease progression date (if it had not occurred yet) and/or exitus. Likewise, treatment lines received in the follow-up were recorded.

- Evaluations:
  - Efficacy (response rate, progression-free survival, duration of response and survival) and safety data were collected. Researchers assessed treatment responses.
  - When disease progression or unacceptable toxicity were observed patients underwent a follow-up phase in which every 12 weeks information about subsequent lines of treatment and survival was collected.

Number of Subjects:

No. Planned: 53

No. Treated: 28

Males/females: 16/12

Average age (range): 76.4 (70-83)

No. Analysed for efficacy (ITT/PP): 28/21

No. Analysed for safety: 28

No. of discontinued patients:

Progression: 16 (57.1%)

Death: 3 (10.7%)

Adverse event: 2 (7.1%)

Patient's decision: 1 (3.6%)

Deviation from the protocol: 2 (7.1%)

Other reasons: 4 (14.3%)

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

- Signing of written informed consent before any specific procedure of the study
- Histological diagnosis of colorectal carcinoma.
- Patients ≥ 70 years.
- Unresectable and/or inoperable metastatic colorectal carcinoma.
- Presence of at least one bidimensionally measurable lesion. Index lesions should not be in a previously irradiated area.
- Karnofsky performance status ≥ 80% at the time of inclusion in the study.
- Life expectancy greater than 3 months.
- Tumour tissue availability for immunohistochemical analysis of EGFR expression.
- Patients had not received chemotherapy for advanced/metastatic disease. Patients with

the following characteristics were included:

a. Recurrence after neo-adjuvant and/or adjuvant treatment with 5-fluorouracil/folinic acid or capecitabine. Patients also could have been treated or untreated with radiotherapy. They should have had a disease-free interval greater than 12 months after treatment completion. Patients were not accepted if they have received adjuvant therapy with combinations of oxaliplatin and/or irinotecan, regardless of recurrence-free interval.

b. Recurrence after surgical treatment and/or radiotherapy without adjuvant systemic therapy.

c. Diagnosis of *de novo* metastatic disease.

- Adequate bone marrow reserve:
  a. Hemoglobin ≥ 9 g/dl
  b. Absolute number of neutrophils ≥ 2.0 x 10^9/l.
  c. Platelet count ≥ 100 x 10^9/l.
- Adequate renal function, defined as a creatinine clearance ≥ 30 ml/min measured by Cockcroft-Gault formula.
- Adequate hepatic function:
  a. Total bilirubin < 1.5 x ULN.
  b. AST (SGOT) and/or ALT (SGPT) and/or alkaline phosphatase ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases).

Exclusion Criteria

- Brain and/or leptomeningeal metastasis, documented or suspected.
- Surgery (excluding biopsy for diagnosis) and/or radiotherapy in the 4 weeks prior to inclusion in the study.
- Concomitant chronic systemic treatment with immunotherapy, chemotherapy or hormone therapy for cancer.
- Previous administration of monoclonal antibodies, inhibitors of EGFR signal transduction or treatment directed at EGFR.
- Participation in another study with medication in the last 30 days.
- Previous participation in a study that included the possibility of being assigned to a treatment with cetuximab (whether treatment with cetuximab was received or not).
- Previous malignant tumour in the last 5 years, except for a history of skin basal cell carcinoma or pre-invasive carcinoma of the cervix.
- Malabsorption syndrome, loss of upper gastrointestinal tract integrity or chronic inflammatory bowel disease, complete or partial bowel obstruction or other conditions

that could alter the absorption of the drug, according to the researcher's opinion.

- Known grade 3 or 4 allergic reaction to any of the components of treatment or to fluoropyrimidines.
- Clinically relevant peripheral neuropathy.
- Clinically relevant coronary pathology or history of myocardial infarction in the last 12 months or high risk of decompensated heart failure or uncontrolled arrhythmia.
- Severe active infection (requiring intravenous antibiotics) including active tuberculosis and HIV infection diagnosis.
- Known alcohol/drugs abuse.
- Legal incapacity or limited legal capacity.
- Any medical or psychological disorder that did not permit the patient to complete the study or sign informed consent, according to the researcher's opinion.
- Patients classified as fragile or sensitive according to the following criteria:
  - Dependence on one or more daily living activities according to the Katz Activities of Daily Living (ADLs) formal scale.
  - Three or more comorbid conditions by the assessment of the following processes presence: congestive heart failure, valvular heart disease, coronary artery disease, chronic lung disease (obstructive or restrictive), cerebrovascular disease, peripheral neuropathy, chronic renal failure, hypertension, diabetes, concomitant malignancies, collagen vascular diseases, chronic liver disease, and disabling arthritis.
  - Presence of geriatric syndromes: moderate-severe dementia, delusions under stress (urinary or respiratory infection, angina or drugs), moderate-severe depression interfering patient normal activity, frequent falls (3 or more per month), neglect (*who could help him/her in an emergency?*); urinary incontinence in the absence of stress, infection, diuretics, or prostatic hyperplasia; fecal incontinence in the absence of diarrhoea or laxative; osteoporotic fractures of long bones or vertebral collapse.

Test Product(s): Dose and Mode of Administration, Batch Number(s):

CETUXIMAB

Pharmaceutical form: 50 ml vials (injectable solution)

Method of administration: intravenous

Concentration: 5 mg/ml

Regimen: initial dose of 400 mg/m^2 (80 ml/m^2) and then weekly doses of 250 mg/m^2 (50 ml/m^2)

Duration of Treatment:

Four cycles of treatment with oxaliplatin, capecitabine (Xelox) and cetuximab combination, followed by capecitabine and cetuximab until disease progression, onset of unacceptable drug toxicity or patient consent withdrawal.

Reference Therapy, Dose and Mode of Administration, Batch Number(s): NA

Duration of Treatment: NA

Criteria for Evaluation:

Efficacy:

Radiological studies assessing disease were performed every 6 weeks during the first 6 months of the trial (24 weeks) and then every 12 weeks until the end-of-study (EOS) visit. In the event that the treatment was permanently stopped without disease progression, radiological assessment was carried out and the patient remained in the study without treatment until disease progression was observed.

The response rate and progression-free survival were evaluated using the modified WHO criteria.

Safety:

Safety was assessed using the Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI), version 3.0.

Statistical Methods: Descriptive analysis.

Summary and Conclusions:

Subject Disposition:

28 patients were included in the study.

Demographics and Baseline Characteristics:

16 men and 12 women, with a mean age (SD) of 76.4 (3.7) years with a Karnofsky performance status ≥ 80%. All participants had been diagnosed with colorectal cancer, localized in the colon in 64.3% of cases and in the rectum in the remaining 35.7%. 75% of patients were EGFR-positive.

Efficacy Results:

With regard to the treatment response, only 7 patients had complete or partial confirmed response in the ITT population. The confirmed response rate was 25.0% (CI 95%: 10.7%, 44.9%) and the disease control rate of 89.7% (CI 95%: 75.8%, 97.1%). In the PP population only 6 patients had complete or partial confirmed response. The confirmed response rate was 28.6% (CI 95%: 11.3%, 52.2%) and the disease control rate was 95.2% (CI 95%: 76.2%, 99.9%).

The median time to response was 3.08 months (94 days) (range, 2.72 - 5.11 months) in the ITT population. The median duration of response was 3.7 months (113 days) (range, 1.54 - 15.02 months) in 7 patients with complete or partial response. The median time to progression was 5.77 months (176 days) (range, 1.21 - 17.70 months).

The median overall survival time was 14.88 months (interquartile range, 7.92 - 19.78 months). The median time to treatment failure was 5.16 months in the ITT population (interquartile range, 3.52 - 9.5 months). The median time of progression-free survival was 5.78 months (interquartile range, 4.21 - 9.79 months). Significant differences in progression-free survival according to the toxicity grade of acneiform skin rash in the PP population were not observed (p> 0.05).

As for the parallel study which explored possible genetic and protein factors predictive of treatment response and/or resistance, it is required a prudent interpretation of results and statistical analyses performed, because of the low sample size. All patients with a result of molecular analysis of B-RAF gene (n= 21) had wild-type B-RAF tumour. No patient showed a loss of PTEN expression.

Concerning the K-RAS gene, the response rate was 42.9% (CI 95% 9.9%, 81.6%) in the 7 patients with wild-type KRAS tumour and 14.3% (CI 95%: 1.8%, 42.8%) in 14 patients with mutated KRAS tumour.

	K-RAS wild type (n= 7)	**K-RAS mutated (n= 14)**
Response		
Complete Response (CR)	1 (14.3%)	1 (7.1%)
Partial Response (PR)	2 (28.6%)	1 (7.1%)
Stable Disease (SD)	4 (57.1%)	11 (78.6%)
Disease Progression (DP)	0 (0.0%)	1 (7.1%)
Non evaluable	0 (0.0%)	0 (0.0%)
Response Rate (CR+PR)		
Response Rate	3 (42.9%)	2 (14.3%)
Confidence Interval (95%)	[9.9%, 81.6%]	[1.8%, 42.8%]
Disease Control Rate (CR+PR+SD)		
Disease Control Rate	7 (100%)	13 (92.9%)
Confidence Interval (95%)	[59.0%, 100%]	[66.1%, 99.8%]

The median time to progression was 8.52 months (260 days) (range, 3.48 - 11.31 months) in 5 patients who progressed with native tumour KRAS and 4.77 months (145.5 days) (range, 1.21 - 17.7 months) in 14 patients who progressed with mutated KRAS tumour.

The median time of progression-free survival was 9.5 months (interquartile range, 8.31 - 11.34 months) in patients with wild-type KRAS tumour and 4.63 (interquartile range, 4.21 - 9.79 months) in patients with mutated KRAS tumour. No statistically significant difference in progression-free survival according to the mutational status of K-RAS gene was observed (p> 0.05).

The response rate was 31.3% (CI 95%: 11.0%, 58.7%) in 16 patients with wild-type PI3KCA tumour. Complete or partial response in patients with mutated PI3KCA tumour was not observed. The median time to progression was 4.77 months (145.5 days) (range, 2.59 - 17.7 months) in 14 patients who progressed with wild-type PI3KCA tumour and 8.3 months (253 days) (range, 1.21 - 10.72 months) in 5 patients who progressed with mutated PI3KCA tumour. The median time of progression-free survival was 4.93 months

(interquartile range, 4.21 - 11.34 months) in patients with wild-type PI3KCA tumour and 8.31 months (interquartile range, 5.16 - 9, 54 months) in patients with mutated PI3KCA tumour. No statistically significant difference in progression-free survival according to the mutational status of PI3KCA was observed ($p > 0.05$).

Among patients with the result of molecular analysis of EGFR gene copy number, only two presented between 5 and 6 copies. Neither of the two patients with 5-6 copies of EGFR gene had progressed, so comparison of time to progression and progression-free survival according to EGFR gene copy number could not be accomplished.

Safety Results:

All patients included in the study had at least one adverse event (AE). One patient died due to a non-treatment related AE. In total, 25 (89.3%) patients had at least one AE related with cetuximab, 26 (92.9%) had at least one AE associated with oxaliplatin and 26 (92.9%) patients had at least one AE associated with capecitabine.

In total, 11 (39.3%) patients had a serious adverse event (SAE), 2 (7.1%) patients had at least one SAE related to oxaliplatin and 6 (21.4%) patients had at least one of SAE related to capecitabine. No patient had a SAE related to cetuximab.

Regarding the grade of the AEs, 22 (78.6%) patients had grade 3-4 AEs according to NCI-CTC. A total of 8 (28.6%) patients had grade 3-4 AEs related to cetuximab, 10 (35.7%) patients had grade 3-4 AEs related to oxaliplatin and 17 (60.7%) patients had Grade 3-4 AEs associated with capecitabine.

AEs led to cetuximab treatment discontinuation in 7 (25%) patients and AEs related to cetuximab caused discontinuation in 2 (7.1%) patients. Whereas, 6 (21.4%) patients discontinued oxaliplatin treatment due to AEs and in 5 (17.9%) patients, the discontinuation cause was AEs related to oxaliplatin. In 8 (28.6%) patients AEs were the cause of discontinuation of capecitabine treatment, and in 7 (25%) patients, the discontinuation cause was AEs related to capecitabine.

According to SOC, the highest incidence AEs in the 28 patients in the safety population were gastrointestinal disorders (n= 25, 89.3%), nervous system disorders (n= 25, 89.3%) disorders, general disorders and administration site conditions (n= 24, 85.7%), and skin and subcutaneous tissue disorders (n= 24, 85.7%).

Whereas according to PT, the highest incidences AE were neurotoxicity and acneiform skin rash, both present in 23 (82.1%) patients. Afterwards, the most frequent AEs were asthenia and diarrhoea, present in 21 (75%) and 18 (64.3%) patients, respectively.

From the 28 patients included in the study, 15 (53.5%) were deceased at its end. The cause of death was disease progression in 14 patients and intercurrent disease unrelated (reported as a SAE) in 1 patient (patient 804-1 presented with acute arterial ischemia of the left leg).

Conclusions:

Cetuximab treatment with Xelox combination in elderly patients with mCRC has toxicity in the high range according to combination chemotherapy in elderly literature.

According to the study design, the first 24 evaluable patients were analysed in a first stage, but the required number of responses (greater than 7) was not reached. In this regard, and due to cetuximab approval as first-line treatment for mCRC patients with the wild-type KRAS gene, the design of the study and the sample size were no longer appropriate in order to determine the efficacy of the proposed treatment regimen. In conclusion, as explained above, the sponsor found justified the premature end of the study with the proposed design.
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