Clinical Report

Section 1 – Title page

Title of Study

Phase II study with a combination of Irinotecan, Capecitabine (Xeloda®) and Bevacizumab (Avastin®) in non-pretreated metastatic colorectal cancer.

Investigational product:	Irinotecan, Capecitabina (Xeloda®) and Bevacizumab (Avastin®)
Clinical trial code:	TTD-08-03
EudraCT number:	2008-004688-20
Development phase:	Phase II
Indication:	Metastatic colorectal cancer
First patient enrolled (date):	April 17th 2011
Last patient visit (date):	May 23rd 2012
Study coordinator(s):	Dr Pilar García Alfonso Oncology Service Hospital Universitario Gregorio Marañón C/Doctor Esquerdo, 46 28007. Madrid. Spain Dr Enrique Aranda Aguilar Oncology Service Hospital Universitario Reina Sofía Av. Menéndez Pidal s/n 14004. Córdoba. Spain

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The present study was carried out in compliance with the Harmonized Tripartite Standards of the International Conference on Harmonisation (ICH) for Good Clinical Practices 1996

Section 2 – Synopsis

Title of study Phase II study with a combination of Irinotecan, Capecitabine (Xeloda®) and Bevacizumab (Avastin®) in non-pretreated metastatic colorectal cancer.
Development phase Phase II
Sponsor Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)
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Publication (Reference) P. Garcia-Alfonso, M. Chaves, A. Muñoz, A. Salud, M. García Gonzalez, C. Grávalos, B. Massuti, E. González- Flores, B. Queralt, A. López-Ladrón, F. Losa, Mª J Gómez, A. Oltra and E. Aranda. Capecitabine and irinotecan with bevacizumab 2-weekly for metastatic colorectal cancer: The phase II AVAXIRI study. BMC Cancer 2015, 15:327.
Study period First patient enrolled: April 17th 2011 Last patient visit: May 23rd 2012
Objectives Primary objective: • To evaluate progression-free survival at 9 months of treatment.

Secondary objectives:

- Overall survival
- Responses rate
- Duration of the response
- Resection rate of liver metastases
- Safety analysis
- Quality of life of patients treated with the study regimen
- Determine the prognostic value of the *K-ras* gene mutation

Methods

Phase II, randomized, open-label, multicentre study to evaluate the efficacy and safety of combined treatment in the first line with irinotecan, capecitabine and bevacizumab in patients with metastatic colorectal cancer (mCRC). The treatment was administered until disease progression, unacceptable toxicity or withdrawal of the patient or withdrawal of it by any of the criteria specified in the protocol as withdrawal criteria.

Number of patients (planned and analysed)

Expected patients: n = 79

Patients included: n = 81

Patients treated: n = 77

Patients analysed: n = 77

Screening failures: n = 4; admission prior to treatment by occlusion, n = 1; non-compliance with selection criteria, n = 3.

Main selection criteria

Inclusion criteria:

1. Metastatic colorectal carcinoma histologically demonstrated.

2. Absence of possibility of initial full surgery.

3. Absence of previous chemotherapy treatment, except for adjuvant treatment completed at least 6 months before its inclusion in the study.

4. Age ≥ 18 years.

5. Performance status (ECOG) ≤ 2

6. Life expectancy ≥ 3 months.

7. Creatinine clearance (> 30 ml/min according to the Cockcroft and Gault formula).

8. Measurable disease according to the RECIST criteria (1).

Exclusion criteria:

1. Previous systemic treatment for the treatment of advanced or metastatic disease.

2. In the case of having received adjuvant treatment, it is not allowed to have progressed during the same or during the 6 months after its completion.

3. If the patient has received radiotherapy, it must not have been administered over the

selected target lesion for the study and must have ended at least 4 weeks before the start of the study.

4. Previous surgical treatment of stage IV disease is allowed.

5. Other neoplastic disease during the past five years (except basal cell carcinomas) of the skin and cervix *in situ*).

6. History or signs of diseases of the central nervous system.

7. Clinically significant (active) cardiovascular disease (uncontrolled hypertension, unstable angina, Congestive heart failure grade II or higher of the New York Heart Association (NYHA), arrhythmias cardiac conditions that require mediation, or peripheral vascular disease grade II or higher) or have suffered a heart attack in the year prior to the start of the study.

8. Lack of physical integrity of the upper gastrointestinal tract, malabsorption syndrome or inability to take oral medication.

9. Intercurrent infections not controlled; severe or other severe concomitant diseases and not controlled.

10. Severe or severe renal insufficiency (creatinine clearance less than 30 mL/min (calculated with the formula Cockroft-Gault) or serum creatinine >1.5 times the upper limit of normal (ULN).

11. Any of the following laboratory values: absolute neutrophils count <1.5 x 10^9/L; platelets <100 x 10^9/L; haemoglobin <9 g/dL (can be transfused to maintain or exceed this level); INR >1.5.

12. Total bilirubin >1.5 times the ULN.

13. ALAT (SGPT) and/or ASAT (SGOT) >2.5 x ULN or >5 x ULN in case of liver metastases.

14. Alkaline phosphatase >2.5 x ULN or >5 x ULN in case of liver metastases, or >10 x ULN in case of bone metastases.

15. Major surgery procedures, open biopsies or significant traumatic injuries within 28 days before the start of the study treatment. Aspirated with a fine needle in the 7 days prior to beginning of the study. Planned major surgery procedure planning during the study period.

Investigational product, dose and regimen, batch number

The treatment under study is bevacizumab in combination with capecitabine and irinotecan.

- **Bevacizumab** was administered at a dose of 5 mg/kg on day 1 of each 2-week cycle.

- **Capecitabine** was administered at a dose of 1000 mg/m^2/every 12 hours (total daily dose: 2000 mg/m^2) orally, on days 2 to 8 of each cycle, with one week of rest after, every 2 weeks. In those older than 65 years, the maximum dose to be administered was 800 mg/m^2/12 hours.

- **Irinotecan** was administered at a dose of 175 mg/m^2 diluted in 250 c.c. of 0.9% physiological saline, in intravenous infusion of 90 minutes, on day 1 of each 2-week cycle.

All study drugs are approved for the treatment of metastatic colorectal cancer, so commercial medication was used. Each centre prescribed and used the study drugs in their commercialized forms and following the usual pathways established in each centre.

Control treatment, dose and regimen, batch number

Not applicable

Duration of treatment

The patients received the study treatment until disease progression manifested or it was necessary the premature abandonment of the patient due to unacceptable toxicity or for any of the reasons specified in the protocol as withdrawal criteria.

Evaluation criteria – Efficacy

Main efficacy parameter:

- Progression free survival (PFS) at 9 months of treatment. PFS was defined as the time elapsed from the start of treatment until the patient progresses or dies from any cause, whatever happens first. In the case of patients who had not progressed or died, the last available follow-up was considered the last control.

Secondary efficacy parameters:

As part of the evaluation of efficacy, the following secondary variables were also collected: time to progression, response rate, time to response, duration of response, time to treatment failure, overall survival, disease-free survival, rate of resection of hepatic metastases and quality of life of the patients.

- *Objective responses*: the objective response of the measurable disease was evaluated according to the criteria RECIST (1), through diagnostic imaging studies: conventional computerized axial tomography (CAT), helical CAT, nuclear magnetic resonance or chest x-ray (documentation of the target and non-target lesions). The response obtained was confirmed with a new evaluation of the response carried out in a period of not less than 4 weeks from the date on which the response criteria. Tumour disease was evaluated at the baseline visit (in the 28 days prior to the administration of the first dose of the study treatment), every 6 cycles during the treatment phases, at the end of the treatment (end of treatment visit), and every 3 months during the monitoring of survival after the end of treatment. The response to treatment was assigned as a complete response (CR), partial response (PR), stable disease (SD) and disease progression according to the RECIST criteria.
- *Time to progression*, defined as the time elapsed from the start of treatment until disease progression was registered for the first time or until the date of the last follow-up.
- *Time to treatment failure*, defined as the time from the start of treatment to the time when the patient leaves the study due to: adverse events (AE), progressive disease/insufficient therapeutic response or death, or because the patient does not goes to the scheduled visits and refuses to receive treatment, does not collaborate or withdraws his consent.
- *Overall survival*, defined as the time elapsed from the start of treatment until the date of death of the patient or until the last control available.
- *Disease-free survival*, defined as the time from when the patient reaches a complete

response until the patient progresses or dies due to the disease (the first thing that happens). In the rest of patients, it was considered the time until the last control available.

- *Time to response*, defined as the time that elapses from the start of treatment until the date on which the response is manifested (CR or PR of measurable disease).
- *Duration of the response*, defined as the time from when a response is reached (CR or PR) until the patient progresses or dies due to the disease, the first thing that happened.
- *Quality of life*, assessed through the EuroQoL questionnaire, which analyses five different dimensions (mobility, personal care, daily activities, pain and mood) each with three categories. In addition, the self-assessed general state of health was recorded using a vertical scale of 20 cm, from 0 ("worst imaginable health status") to 100 ("best imaginable health status"), divided into 10 out of 10 categories.

Evaluation criteria – Safety

In order to evaluate the safety of the treatment, all the AEs reported during the study were recorded (from the signing of the informed consent until 28 days after the last dose of treatment administered), collecting information on the maximum intensity, the causal relationship with the study treatments, the duration and the resolution of it. The AEs were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI), version 3.0 (2).

Statistical methods

Justification of the sample size calculation

Applying the model proposed by Fleming (Fleming, 1982) for the design of Phase II studies (Single Stage Procedure) and assuming as a minimum value, below which the treatment is discarded, a rate of progression-free patients (P0) of 12% at two years (equivalent to a median PFS of 8 months) and an optimal P1 value of 25% (equivalent to a median of PFS of 12 months), with an alpha error (probability of declaring the treatment active if the true percentage of responses is equal to or less than P0) of 0.05 (unilateral), and a beta error (probability of rejecting the drug if the true percentage of responses is compatible with P1) of 0.1 (power of 90%), it was estimated that the sample size of the trial should be 71 evaluable patients. To obtain the 71 evaluable patients, considering the possibility of reaching up to 10% of losses, it was estimated that the number of patients to be recruited in the trial would be 79.

Populations analysed

The following populations were defined for the analysis of the study:

- Intention to treat (ITT) population: defined by the patients treated, that is, those who had received at least one dose of the study medication. N = 77.
- Safety population (SP): defined by the treated patients, that is, those who had received at least one dose of the study medication. N = 77.

Statistical methods

The quantitative variables were described with measures of centralization and dispersion (mean, median, S.D. [standard deviation], Q1 [first quartile], Q3 [third quartile], minimum and maximum). The qualitative variables were described by absolute and relative frequencies. In the descriptive analysis of the qualitative variables, the total percentage (%) and the valid percentage (valid %) are presented, that is, the percentage on the sum of the valid answers plus the values lost and the percentage on the total of valid answers. The 95% confidence intervals (95% CI) were calculated, when necessary. The efficacy analysis was carried out in the ITT population. The response rate was calculated with the percentage frequencies, with a 95% CI. The PFS and overall survival analyses were performed using the Kaplan Meier method, providing the median, mean, CI at 95%, as well as the number of events and number of cases censored. For the comparison of estimated survivals between different subgroups, the logarithmic rank test (Log-rank) was applied and for the comparison of the response rate between different subgroups, the Chi-square test was used. The safety analysis was performed in the SP. The frequency of AE was estimated, which were grouped according to the categories established by CTCAE v3.0 from the original term registered by the researcher. AEs were grouped according to their intensity, and severe AEs were described. The maximum of the grades was calculated for each of the AE collected throughout the treatment cycles of each patient.

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

Demography of the study population

The study population is composed of 77 patients (ITT) with a median age of 65 years (range: 41-81) and 66% of men.

Efficacy results

The median follow-up time of the patients was 23.3 months (range: 0.4-39.6 months). The median PFS was 11.9 months (95% CI: 10.8-13.1 months) with a PFS at 9 months of 61% (95% CI: 48-73). The median time to progression was 11.9 months (95% CI: 10.8-13.1 months).

The median overall survival was 24.8 months (95% CI, 19.9-29.7 months). At the time of the analysis, 45 patients had died (58%). The majority of patients died due disease progression (n= 7, 46%) and 7 patients (9%) died as a result of an AE. The overall response rate (CR + PR) was 51% (95% CI: 39-62%) and the disease control rate was 84% (95% CI: 74–91%), with a median response duration of 9.4 months (95% CI: 7.8-11.1 months). The median time to response was 2.8 months (95% CI, 2.6-2.9 months). The tumour control rate (CR + PR + SD) was 84% (95% CI: 74-91%). The median time to treatment failure was 12.3 months (95% CI: 8.7-15.8 months).

Median progression-free survival was 12.0 months (95% CI: 6.6–17.5 months) in patients with wild-type *KRAS* tumours and 11.8 months (95% CI: 10.7–13.0 months) in those with mutant *KRAS* tumours (P= 0.985). Overall survival was also similar in patients with wild-type and mutant *KRAS* tumours: 28.5 months (95% CI: 21.4–35.6 months) versus 27.9 months

(95% CI: 21.4–34.3 months), respectively (P= 0.659). Confirmed response rates were 44.4% in patients with wildtype *KRAS* tumours and 37.1% in those with mutant *KRAS* tumours (P >0.05).

Seventeen patients (22%) had surgical resection of metastases during the study (65% liver metastases, 18% lung metastases, 12% peritoneal metastases and other sites). The median time to surgery after treatment initiation was 6.7 months. Twelve patients (71%) underwent R0 resection, three (18%) had an R1 resection and two (12%) were not evaluable. Thirteen of the seventeen patients who underwent surgical resection had further treatment (chemotherapy or immunotherapy).With respect to second-line chemotherapy six patients received post-surgical treatment with bevacizumab plus capecitabine/irinotecan and three patients received other bevacizumab containing regimens. The remaining patients received avariety of other regimens that included oxaliplatin, cetuximab and panitumumab.

Safety results

All patients experienced at least one AE during the study. A total of 1436 AEs were recorded in 77 patients. The majority of patients (99%) experienced at least one AE related to the study treatment remotely, possible, probable or unknown. Of all patients, 48 (62%) had at least one AE grade 3 or 4, considered to be related to the study medication in 45 patients (62%). The most frequent grade 3-4 AEs, reported in more than 5% of patients, were diarrhoea (18%), asthenia (17%), pulmonary thromboembolism (13%), neutropenia (10%), febrile neutropenia (6%), intestinal occlusion (6%) and hand-foot syndrome (5%). The presence of serious AEs (SAEs) was reported in 29 patients (38%), considered to be related to treatment in 18 patients (23%). Seven patients (9%) died as a result of an SAE, considered remote, possible or probably related to the study treatment (toxic deaths) in 3 patients.

Quality of life

Patient quality of life did not vary greatly over the study period. Most patients reported having no problems with mobility, patient care or activities of daily living during the first cycles of treatment. More than 50% of patients experienced pain or discomfort in the early cycles, although this proportion decreased as the study progressed. More than half of all patients reported feeling moderately or very anxious, or depressed throughout the study period. Mean VAS general health scores ranged from 71 to 76 over cycles 1–11.

Conclusions

The results of the AVAXIRI study support the use of irinotecan and capecitabine administered every 2 weeks in combination with bevacizumab in patients with mCRC. This study included patients with multiple comorbidities and elderly patients, and therefore indicates that this is an effective and tolerable regimen.

Date of issue

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