CLINICAL STUDY REPORT

A PHASE II CLINICAL TRIAL OF PANITUMUMAB IN COMBINATION WITH IRINOTECAN CHEMOTHERAPY AS SECOND-LINE THERAPY IN SUBJECTS WITH METASTATIC COLORECTAL CANCER.

Sponsor:	Grupo de Tratamiento de los Tumores Digestivos (TTD) [Spanish Cooperative Group for the Treatment of Digestive Tumors]
Study code:	TTD-06-04
EudraCT No.:	2006-006363-24
Study phase:	II
Date of final report:	05/10/2011
Version:	Final
First patient in (date):	11/06/2007
Last patient in (date):	25/08/2008
Coordinating investigator of the study:	Dr. Alfredo Carrato
Sponsor's representative:	Inma 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. 2006-006363-24	(For the health authorities only)
Name of medicinal product: VECTIBIX®		
Name of the active substances: Panitumumab		

Trial title: A phase II clinical trial of panitumumab in combination with irinotecan chemotherapy as second-line therapy in subjects with metastatic colorectal cancer.

Investigators:
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Publication (reference):
A. Carrato A. Gómez, P. Escudero, M. Chaves, F. Rivera, E. Marcuello, E. González, C. Grávalos, M. Constenla, JL. Manzano, F. Losa, J. Maurel, R. Dueñas, B. Massuti, J. Gallego, J. Aparicio, A. Antón and E. Aranda on behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD) Panitumumab and irinotecan every 3 weeks is an active and convenient regimen for second-line treatment of patients with wild-type K-RAS metastatic colorectal cancer
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CONGRESS
A. Carrato, A. Gomez, P. Escudero; M. Chaves, F. Rivera, E. Marcuello, E. González Flores, C. Grávalos, M. Constenla, E. Aranda. Panitumumab plus irinotecan, both given every three weeks (Q3W), as second-line treatment for irinotecan-naïve metastatic colorectal cancer (mCRC).
American Society of Clinical Oncology (ASCO) Annual Meeting Proceedings. J Clin Oncol 28, 2010 (suppl; abstr e14025)

A. Gomez, P. Escudero, M. Chaves, F. Rivera, E. Marcuello, E. González Flores, C. Grávalos, M. Constenla, E. Grande, E. Aranda. Efficacy and safety of second-line treatment with panitumumab plus irinotecan, both given every three weeks (Q3W), in patients (pts) with wild-type (WT) K-RAS metastatic colorectal cancer (mCRC): A study from the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD).
35th Congress of the European Society for Medical Oncology (ESMO). PD 583. Annals of Oncology, Volume 21 (Supp 8):190. 2010

E. Aranda, A. Gómez, P. Escudero, M. Chaves, N. Vega, E. Marcuello, E. González Flores, C. Grávalos, M. Constenla, A. Carrato. Eficacia y seguridad del tratamiento en segunda línea con panitumumab más irinotecan, administrados cada tres semanas (Q3W), en pacientes (pts) con K-RAS de tipo nativo (WT) y cáncer colorrectal metastático (CCRm): Estudio del Grupo de Tratamiento de los Tumores Digestivos (TTD)
XIII Congreso Nacional de la Sociedad Española de Oncología Médica (SEOM). O-8. 2011

Study period (years): 2007-2010	**Study phase:** Phase II clinical trial

Objectives:
Primary objective:
- To assess the objective response rate (ORR) when panitumumab is administered in combination with irinotecan as second-line therapy in subjects with metastatic colorectal cancer (mCRC)

Secondary objectives:
- To evaluate the combined therapy of panitumumab and irinotecan with other efficacy measurements: disease control rate (DCR), duration of response (DR), time to response (TTR), progression-free survival (PFS), overall survival (OS) and time to progression (TTP).
- To evaluate the safety profile of the combination of panitumumab and irinotecan.

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- To evaluate the efficacy and safety of the combined therapy of panitumumab and irinotecan, followed by a monotherapy of panitumumab or irinotecan for the subjects that interrupt irinotecan as second-line therapy of a previously treated metastatic colorectal cancer.

Exploratory objectives:

- Parallel study of biomarkers as possible predictive factors of response and/or resistance to treatment, such as the number of copies of EGFR gene, the protein expression of PTEN, the mutations in the EGFR, PI3K, K-RAS and B-RAF genes, and the expression of epirregulin and anfirregulin.
- Other exploratory objectives include the research of the patients notified results measurements (PRO), the use of sanitary attention and a scheme of treatment of the ocular toxicity and tegumentary, to the combined therapy of panitumumab and chemotherapy, followed by the optional monotherapy of panitumumab to the subjects that interrupt chemotherapy as the second-line treatment to a previously treated mCRC.

Methodology:

Phase II, open-label, multi-centre, single-arm study. This study designed in a single group allowed the efficacy and safety determination of the panitumumab administration every three weeks with and standard second-line therapy in subjects with metastatic colorectal cancer. The eligible patients were included and received the combined second-line therapy of panitumumab with irinotecan chemotherapy.

Prior to study entry and in order to confirm eligibility, the investigator or designee reviewed existing radiological images in addition to any other relevant clinical documents (reports, notes, etc.) to ensure the subject had failed or relapsed while on or after one prior chemotherapy regimen.

Panitumumab was administered by intravenous infusion (IV) at a dose of 9mg/kg once every three weeks, the day 1 of each cycle of 21 days (± 3 days). The irinotecan chemotherapy was administered after the administration of panitumumab. Subjects were permitted to receive the combination panitumumab and chemotherapy until disease progression (DP) or unacceptable toxicitiy. Subjects were permitted to receive monotherapy of panitumumab or irinotecan until the disease progression or the presence of unacceptable toxicity. The treatment period ended after the discontinuation of panitumumab and the subjects must attend a safety follow-up visit 56 ± 3 days later.

Number of patients (planned and analysed):

	Patients	**Mutated K-RAS**	**Wild-type**
K-RAS			
No planned .	80		
No. treated	85	18	53
Men/women	55/30	10/8	35/18
Average age (range) (37-83)	63,5 (37-83)	63,6 (44-74)	64,7
No. Analysed for efficacy (ITT/PP)	85	18	53
No. Analysed for safety	85	18	53
Number of patients discontinued	85	18	53
Progression	11 (61.11%)	32 (60.38%)	51 (60.00%)
Toxicity	2 (11.11%)	6 (11.32%)	8 (9.41%)
Death	1 (5.56%)	6 (11.32%)	7 (8.24%)
Withdrawal of consent by the patient	0 (0.00%)	0 (0.00%)	0 (0.00%)
Potential Adverse Event	1 (5.56%)	1 (1.89%)	2 (2.35%)
Other reasons	1 (5.56%)	1 (1.89%)	3 (3.53%)
Possible surgical rescue evaluation	0 (0.00%)	4 (7.55%)	8 (9.41%)
Researcher opinion (no benefit of the therapy)	1 (5.56%)	2 (3.77%)	4 (4.71%)
Patient refuse more chemotherapy	1 (5.56%)	1 (1.89%)	2 (2.35%)

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Diagnosis and main inclusion criteria:

Inclusion criteria:

1. Man or woman > 18 years of age
2. Competent to comprehend, sign, and date an IEC-approved informed consent form.
3. Histologically or cytologically-confirmed metastatic adenocarcinoma of the colon or rectum by the researcher in subjects with metastatic disease, with wild-type KRAS.
4. Radiographically documented disease progression per modified RECIST criteria while either receiving or ≤ 6 months after the last dose of prior first-line chemotherapy for mCRC.
5. At least one uni-dimensionally measurable lesion of at least 20 mm per modified RECIST criteria (all locations of the disease must be evaluated ≤ 28 days before the inclusion).
6. If subject has prior history of cancer other than colorectal carcinoma, basal cell carcinoma, or cervical carcinoma *in situ*, then subject must not have had treatment or active disease within 5 years.
7. Prior radiotherapy is acceptable, provided that more than 14 days must have elapsed since the last radiotherapy administration and the early toxicity signs must have abated.
8. One and only one prior chemotherapy regimen for mCRC consisting of first-line oxaliplatin-based chemotherapy.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
10. Life expectancy ≥ 3 months.
11. Hematologic function (within the 7 days of the beginning of study treatment):
    - Absolute Neutrophil Count (ANC) > 1,5 x 109/l
    - Platelet count > 100 x 109/l
    - Haemoglobin > 10 g/dl
12. Renal function (within the 7 days of the beginning of study treatment)
    - Creatinine < 1,5 mg/dl
13. Hepatic function(within the 7 days of the beginning of study treatment):
    - Aspartate aminotransferase (AST) < 3 x ULN (if liver metastases ≤ 5 x ULN)
    - Alanine aminotransferase (ALT) < 3 x ULN (if liver metastases ≤ 5 x ULN)
    - Bilirubin < 2 x ULN

Exclusion criteria:

1. More than one prior chemotherapy regimen for mCRC consisting of first-line oxiplatin-based chemotherapy.
2. Systemic chemotherapy, hormonal therapy, immunotherapy or experimental or approved proteins/antibodies (eg, bevacizumab) ≤ 30 days before inclusion.
3. Unresolved toxicities from prior systemic therapy that, in the opinion of the investigator, does not qualify the patient for inclusion.
4. Central nervous system/brain metastases (exception: eligible subjects that have been treated, presented asymptomatic metastases in the central nervous system and had not received steroids within 30 days before the inclusion in the study).
5. Significant cardiovascular disease, including unstable angina or myocardial infarction within 6 months before initiating study treatment or a history of ventricular arrhythmia.
6. Prior anti-EGFr antibody therapy (eg, cetuximab) or treatment small molecule EGFr tyrosine kinase inhibitors (eg, erlotinib).
7. History of interstitial pneumonitis or pulmonary fibrosis or evidence of interstitial pneumonitis or pulmonary fibrosis on baseline chest CT scan.
8. Treatment for systemic infection within 14 days before initiating study treatment.
9. Radiotherapy ≤ 14 days prior to inclusion. Patients must have recovered from all radiotherapy-related toxicities.
10. Active inflammatory bowel disease or other bowel disease causing chronic diarrhoea (defined as > 4 loose stools per day).
11. History of Gilbert's syndrome or dihydropyrimidine deficiency.
12. History of any medical condition that may increase the risks associated with study participation or may interfere with the interpretation of the study results.
13. Known positive test for human immunodeficiency virus infection, hepatitis C virus, chronic active hepatitis B infection.

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14. Subject allergic to the ingredients of the study medication or to Staphylococcus protein A.
15. Any co-morbid disease that would increase risk of toxicity.
16. Any kind of disorder that compromises the ability of the subject to give written informed consent and/or comply with the study procedures.
17. Any investigational agent within 30 days before the inclusion.
18. Must not have had a major surgical procedure within 28 days before randomization.
19. Woman who is pregnant or breast-feeding.
20. Woman or man of childbearing potential not consenting to use adequate contraceptive precautions, such us the use of double barrier contraceptive methods (eg, diaphragm plus condom) or abstinence during the course of the study and during 6 months after the last administration of the investigational medicine to the women and 1 month to the men.
21. Subject unwilling or unable to comply with study requirements.

Investigational product, dose and dosing regimen, batch number:
PANITUMUMAB
Pharmaceutical form: 10-ml vials (solution for injection)
Route of administration: intravenous
Concentration: 20 mg/ml
Dosing regimen: 9 mg/kg the day 1 of each cycle (1 cycle: 21 ± 3 days).

Treatment duration:
Patients received combined therapy until disease progression or development of unacceptable toxicity. Patients could receive monotherapy of panitumumab or irinotecan until disease progression or development of unacceptable toxicity.

Evaluation criteria:
Efficacy endpoints:
Tumour response was evaluated by the investigator according to the modified Response Evaluation Criteria in Solid Tumours (RECIST). Tumour response of the subjects was evaluated every 9 weeks ± 1 week until disease progression or treatment withdrawal. Responding disease was confirmed in no less than 28 days after the criteria for response are first met. In subjects with symptoms suggestive of disease progression, tumour progression must be evaluated at the time that symptoms occur.
Subjects completed an EQ-5D PRO questionnaire every 6 weeks ± 1 week, from baseline through to the end of the treatment period and at the safety follow-up visit.

Safety assessments:
Safety was evaluated using the National Cancer Institute's (NCI) Common Toxicity Criteria (CTC), version 3.0.

Statistical methods:
Statistical analyses were conducted on the intention-to treat (ITT) population, which include all the patients in the study who received a therapy dose and presented at least one baseline measurable lesion. Safety analysis were performed in the safety population (SP), which include all the patients who received at least one dose of therapy.
In general, the results are presented summarized with descriptive statistics. Demographic data, baseline characteristics, efficacy and safety results are summarized in stratified tables depending on the mutational status of the K-RAS gene in the ITT and SP population. For both populations, the total values are showed for both patients with evaluated K-RAS (mutated + wild-type) as well as the total patients included in the population.

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RESULTS/CONCLUSIONS SUMMARY

Efficacy results:

The main purpose of the study is to assess the objective response rate when panitumumab is administered in combination with irinotecan as second-line therapy in subjects with metastatic colorectal cancer.

87 patients were included in the study, two patients did not take the medication of the study therefore they were not included either in the safety population or in the efficacy population (ITT population). In the patients who were possible to evaluate the mutational status of K-RAS gene, a total of 18 patients presented K-RAS mutated tumours and 53 patients presented wild-type K-RAS tumours.

The safety population/ITT was constituted of 55 men and 30 women (35 and 18 respectively in the wild-type K-RAS patient subgroup). The median age of this population was 66 years (range 37-83) (the median age was 67 years in the wild-type K-RAS patient subgroup).

Most of the patients, n=79 (92.9%), presented a prior surgery to the colorectal cancer (n= 48, 90.6% of the patients with wild-type K-RAS). The most frequent prior chemotherapy regimen within the included patients in the study was FOLFOX (37.7%). In only one patient (wild-type K-RAS) the study lesions had been previously irradiated.

For the overall population, the objective response rate was 22.4% (IC95%: 14.0%-32-7%). In wild-type K-RAS patients, the objective response rate was 22.6% (IC95%: 12.3%-36.2%). There was no reported completed response as a better global response in this subgroup of patients. A higher percentage of patients with partial response was observed in the patients with acneiform skin rash of grade ≥ 2 than in the patients who did not present this AA or had a grade 1. The control rate of the disease was 61.2% (IC95%: 50.0%-71.6%). In patients with wild-type K-RAS tumours this tax was 64.2% (IC95%: 49.8%-76.9%).

The median overall duration of the response was 6.2 months. In patients with wild-type K-RAS (in all of the cases a partial response) the median duration of the response was 4.96 months (interquartile range, 3.42-7.85 months). The median of the time until the response was 4.39 months (4.36 months [range, 3.81-5.09 months]) in patients with wild-type K-RAS.

Furthermore, the median of the time until the progression in patients with wild-type K-RAS was 4.63 months (interquartile range, 2.14-9.43 months). The median of the time of progression-free survival was 4.47 months (interquartile range, 2.07-8.44 months). Finally, the median of the overall survival in patients with wild-type K-RAS was 15.08 months (interquartile range, 4.50-22.54 months).

Safety results:

All the patients presented some type of adverse event (AE). The 82.4% (n=70) of the patients presented some AE of grade 3 or 4. The 96.5% (n=82) of the patients presented at least one AE related to panitumumab and/or irinotecan. The 71.8% (n=61) of the patients presented at least one AE of grade 3 or 4 related to the treatment. Seven patients died due to an AE, in 3 patients the AE was considered related to the treatment. The AEs caused the discontinued treatment of panitumumab and/or irinotecan in 23 (27.1%) patients. The AEs related to the treatment led to a discontinued therapy in 19 (22.4%) patients.

Among patients with wild-type K-RAS, the 86.8% (n=46) presented some AE of grade 3 or 4. The 94.3% (n=50) presented at least one AE related to panitumumab and/or irinotecan. The 73.6% (n=39) of the patients presented at least one AE of grade 3 or 4 related to panitumumab and/or irinotecan. In this subgroup of patients, 5 deaths were reported due to some type of AE, in two patients the AE was considered related to the study therapy. In patients with wild-type K-RAS the AEs led to a discontinued therapy in 14 (26.4%) cases. The AEs related to the treatment led to a discontinued therapy in 12 (22.6%) patients.

According to SOC, the AEs with more incidence in the 53 wild-type K-RAS patients were gastrointestinal disorders (n= 51, 96.2%), skin and subcutaneous disorders (n= 45, 84.9%) and general disorders and variations in the site of administration (n= 44, 83%). According to PT, the most frequent AE was diarrhoea present in 44 (83%) of the patients and acneiform skin rash present in 43 (81%) patients.

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CONCLUSIONS

This study shows that the administration of panitumumab plus irinotecan every 3 weeks is safe, active and feasible as second-line treatment in patients with advanced CRC and WT K-RAS CRC.