**Trial title:** Prospective, multicenter, single-arm phase II clinical trial for biomarker validation in patients with advanced and / or metastatic colorectal cancer with KRAS gene not mutated treated with chemotherapy plus biweekly cetuximab as first-line therapy.

**Protocol Code:** GEMCAD-1002

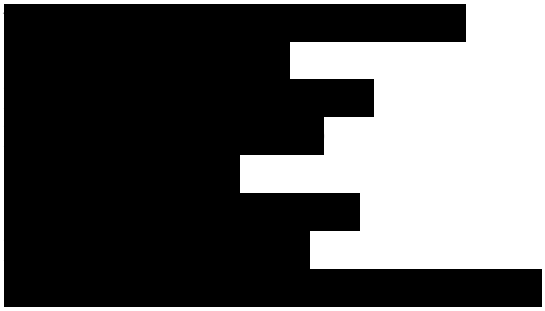
**EudaCT Number:** 2010-019236-12

**Acronym:** POSIBA

**Sponsor:**
Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD)

**Coordinating Investigator:**

**Co-coordinating Investigator:**



**Investigator acceptance**

I have read the attached protocol entitled “Prospective, multicenter, single-arm phase II clinical trial for validation of biomarkers in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS gene treated with chemotherapy plus biweekly cetuximab as first-line therapy”.

I agree to abide by the Guidelines for Good Clinical Practice of the International Conference on Tripartite Harmonization and all applicable regulations / guidelines.

I agree to guarantee that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of clinical research without the prior written consent of the trial sponsor.

**Signature**

**Name of Principal Investigator**
**Principal Investigator site**
**Date**

## 1. Summary

**Title:** Prospective, multicenter, single-arm phase II clinical trial for biomarker validation in patients with advanced and / or metastatic colorectal cancer with KRAS gene not mutated treated with chemotherapy plus biweekly cetuximab as first-line therapy.

**Study Phase:** Phase II

**Indication:**

Advanced and / or metastatic colorectal cancer (CCRA)

**Principal Objective:**

Validation of the biomarkers BRAF, IGF1P / MMp7 (DP) and PI3K-PTEN to predict PFS in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS treated with standard chemotherapy plus biweekly cetuximab as first-line therapy.

**Secondary Objectives:**

Secondary biological markers (MMP-7, IGF-1 and IGFBP3) will be analyzed in serum and tumor tissue to predict acquired resistance.
OS based on proposed classification
Objective response according to RECIST 1.1 (*E.J. Cáncer 2009; 228-47*)
Safety of administration of cetuximab 500 mg / m2 every 2 weeks.

**Clinical Hypothesis:**

Our hypothesis is that the proposed markers will make it possible to select those patients who will benefit the most from biweekly cetuximab treatment.

**Study design:**

Single-arm prospective phase II clinical trial.

Prior to inclusion in the trial and to confirm eligibility, the investigator or designee will review the status of KRAS, BRAF, IGF1P / MMP7 (DP) and PI3K-PTEN, existing radiological images in addition to any other relevant clinical documents ( reports, notes, etc.) to confirm that the subject has previously untreated advanced and / or metastatic colorectal cancer.

FOLFIRI (m) / FOLFOX6 (m) will be administered once every 2 weeks until 6 months of treatment, disease progression (PE), or unacceptable toxicity. Cetuximab will be administered every 2 weeks until disease progression. If patients do not show progression after 6 months of treatment with FOLFIRI (m) and FOLFOX6 (m), they will continue to receive biweekly cetuximab as monotherapy until progression.

Subjects who stop receiving FOLFOX6 (m) / FOLFIRI (m), for example due to toxicity, may receive biweekly cetuximab as monotherapy until disease progression. Following discontinuation of biweekly cetuximab, the treatment period will end and subjects will attend a follow-up safety visit

30 ± 3 days later.

Throughout the trial, subjects will undergo tumor response assessment (using the revised [RECIST 1.1] Solid Tumor Response Assessment Criteria) every 12 weeks (three months) until disease progression. In subjects with symptoms that indicate disease progression, tumor response should be assessed at the time of symptoms.

**Biologic study**

K-RAS, in patients who do not have a determination, and other markers of tumor tissue will be measured at the Navarra University Clinic (CUN) and the markers of the blood samples will be measured at the Hospital Clínic de Barcelona (HCB).
Biomarkers will be measured prior to patient enrollment. In addition, blood samples will be collected every 3 months until disease progression.

**Endpoints:**

**Principal endpoint:**

The main endpoint is progression-free survival comparing two cohorts, which will be defined according to the classification based on the predictive capacity of the response of the biomarkers.

**Secondary endpoint:**

Secondary biological markers in serum and tumor tissue will be analyzed to predict acquired resistance.
OS based on proposed classification
Objective response according to RECIST 1.1 (*E.J. Cancer 2009; 228-47*) (objective response rate)
Response duration
Safety (Type, frequency and intensity of appearance of Adverse Events)

**Sample size:**

A sample size of 170 patients will be needed.

**Principal Inclusion Criteria:**

Patients, men or women aged 18 years or older, with advanced and / or metastatic colorectal cancer with non-mutated KRAS, histologically or cytologically confirmed and radiologically evaluable, ECOG performance status of 0 to 2 with adequate hematological, renal and hepatic function and informed consent signed.

Ver listado completo de Criterios de Inclusión en el apartado 6.1 del protocolo

**Principal Exclusion Criteria:**

Patients who have received prior systemic treatment for metastatic colorectal carcinoma will be excluded from the trial. Patients with previous surgery for metastases (liver, lung or other), metastases in the central nervous system or with significant cardiovascular disease will also be excluded.

Ver listado completo de Criterios de Exclusión en el apartado 6.2 del protocolo

**Dosage and administration of the investigational product:**

FOLFOX6 (m) chemotherapy regimen:

FOLFOX6 (m) chemotherapy will be given on day 1 of each 14-day treatment cycle. FOLFOX6 (m) will be administered at the following doses:

85 mg / m2 of oxaliplatin infusion i.v. 120 minutes on day 1 of each cycle.
400 mg / m2 leucovorin infusion i.v. 120 minutes on day 1.
One i.v. bolus (2 to 4 minutes) of 400 mg / m2 5-FU on day 1.
5-FU in continuous infusion 2400 mg / m2 administered by ambulatory pump over a period of 46-48 hours

FOLFIRI (m):

FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-day treatment cycle. FOLFIRI (m) will be administered at the following doses:

Irinotecan 180 mg / m2 in infusion i.v. 120 minutes on day 1 of each cycle.
Leucovorin 200 mg / m2, in infusion i.v. 120 minutes on day 1.
One i.v. bolus (2 to 4 minutes) of 400 mg / m2 5-FU on day 1.
5-FU in continuous infusion 2400 mg / m2 administered by ambulatory pump over a period of 46-48 hours.

CETUXIMAB:

Administer 500 mg / m2 i.v. every 2 weeks.

It is recommended to administer cetuximab first and start with the administration of FOLFOX6 (m) / FOLFIRI (m), at least one hour after cetuximab administration has ended.

**Statistical considerations:**

Prospective, multicenter, phase II clinical trial designed for the validation of predictive tumor biomarkers in patients with metastatic colorectal cancer and tumor with non-mutated KRAS, treated with chemotherapy and biweekly cetuximab as first-line treatment.
The main objective of this trial is to validate the biomarkers BRAF, IGF1P / MMp7 (DP) and PI3K-PTEN to predict PFS in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS treated with standard chemotherapy plus biweekly cetuximab as therapy. From first line.
Two groups will be defined based on the classification constructed from the clinical variables and the proposed biomarkers.
A minimum difference of 20% (60 vs. 40%) in PFS is expected at 12 months between groups and with the following assumptions:

Alpha error (bilateral): 5%
Beta error: 20%

The number of patients required is 155 patients. Assuming 10% non-evaluable patients, a total of 170 patients will be included.

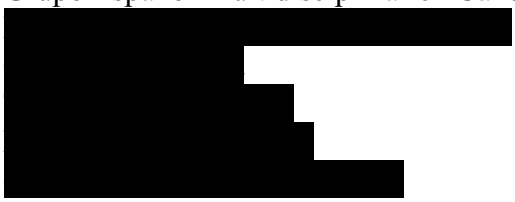
The Cox regression analysis will be performed with the experimental biomarkers and the following prognostic variables (LDH, functional status, age, limited resectable disease (<3 nodules and <5cm). A classification will be performed using the most discriminatory variables. The classification It will be carried out with all the clinical variables of impact in the univariate analysis including the 4 clinical variables (LDH, functional status, age, limited resectable disease <3 nodules and <5 cm) and the 3 pathways previously described (BRAF, DP and PTEN- PI3K) .The classification will be carried out with the variables with the greatest impact in the multivariate analysis.
The proposed sample size ensures the construction of a consistent multivariate analysis.

The analysis of the main variable “progression-free survival comparing two cohorts, which will be defined according to the classification based on the prediction capacity of the response of the biomarkers” and the secondary variable “efficacy”, will be based on the revised version of RECIST 1.1 criteria (Appendix E) for the intention-to-treat analysis group.

Changes in laboratory values and vital signs will be summarized with descriptive statistics.

**Sponsor:**

Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD)



**Name of the Organization responsible for Monitoring:**

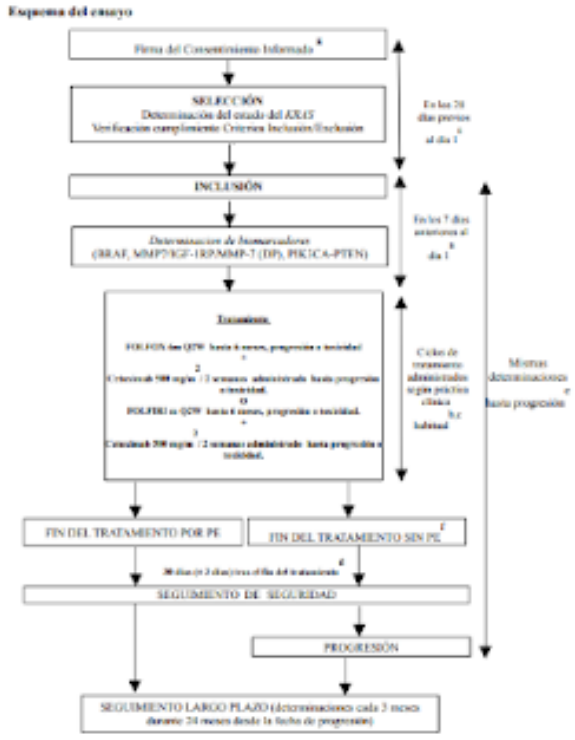
Secretaría Técnica GEMCAD

**Schedule and expected completion date:**

**Start date:** Second quarter 2010
**First Inclusion Date:** Fourth quarter 2010
**Recruitment period:** 24 months
**End of Trial Period:** Year 2014

Single-arm, multicenter, prospective phase II clinical trial for biomarker validation in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS gene treated with chemotherapy plus biweekly cetuximab as first-line therapy

## Study scheme




a Day 1 = day of the first treatment administration.
b Subjects' tumor response will be assessed every 12 weeks, throughout the trial until PE (per revised RECIST 1.1 criteria) or withdrawal from the study.
c Subsequent cycles could be delayed due to toxicities associated with cetuximab or chemotherapy.
d All subjects who permanently discontinue treatment (discontinuation is considered completion of all treatment) for any reason will undergo a follow-up safety assessment 30 days ± 3 days after the last dose of treatment. After the safety follow-up visit, subjects who have not progressed will be followed up every 12 weeks as defined in the study. Subjects who undergo surgery for metastases should follow the controls every 12 weeks as established in the protocol. In case of progression by RECIST 1.1 criteria ,. Subjects will be monitored for disease status, subsequent cancer treatment, and survival (long-term follow-up).
e All subjects who discontinue treatment prior to disease progression (eg, due to unacceptable toxicities) will be followed up for PFS (eg, radiographic tumor assessments) every 12 weeks until the progression of the disease or the end of the study (unless the reason for abandoning the study was the total withdrawal of consent).
F. The end of treatment is understood to be the last day the patient has received the last drug of the combination under test (FOLFOX6 (m) / FOLFIRI (m) / Cetuximab). The safety visit should be carried out 30 ± 3 days after the end of the treatment, regardless of the cause that caused it. If the patient has not progressed, imaging and biomarker determinations should continue every 12 weeks until progression as specified in this protocol.
g. In order to mobilize any biological sample, the signing of the informed consent will be mandatory. If the patient already has a previous determination of the status of the KRAS gene, he can be included in the test without it being necessary to re-determine the mutational status of K-RAS.

## 2. INDEX

## 3. GENERAL INFORMATION

### *3.1 Clinical Trial Identification*

Protocol Code: GEMCAD-1002

Title: Single-arm, multicenter, prospective phase II clinical trial for biomarker validation in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS gene treated with chemotherapy plus biweekly cetuximab as first-line therapy.

N EudraCT: 2010-019236-12

### *3.2 Clinical Trial Type*

Single-arm prospective phase II clinical trial.

### *3.3 Description of the Products under Study*

FOLFOX6 (m)

Oxaliplatin 5 mg / ml powder for solution for infusion.

Leucovorin (CALCIUM FOLINATE). Powder for solution for injection (350 mg of folinic acid).

Fluorouracil (5-FU) solution for injection 50 mg / ml.

FOLFIRI (m)

Irinotecan 20 mg / ml (irinotecan hydrochloride trihydrate) concentrate for solution for infusion (equivalent to 17.33 mg / ml irinotecan).

Leucovorin (CALCIUM FOLINATE). Powder for solution for injection (350 mg of folinic acid).

Fluorouracil (5-FU) solution for injection 50 mg / ml.

CETUXIMAB

Cetuximab (Erbitux®) 2 mg / ml solution for infusion

### *3.4 Sponsor*

Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD)

### *3.5 Coordinating Investigator:*

[redacted]

### *3.6 Co-coordinating Investigator:*

[redacted]

### *3.7 Monitor*

Secretaría Técnica GEMCAD

[redacted]

### *3.8 Sites*

Attachment

### *3.9 Schedule and expected completion date*

**Start date:** Second quarter 2010
**First Inclusion Date:** Fourth quarter 2010
**Recruitment period:** 24 months
**End of Trial Period:** Year 2014

## 4. RATIONALE AND OBJECTIVES

### *4.1 Colorrectal Cancer (CRC)*

Colorectal carcinoma is one of the most common neoplasms in Western countries and is the second most common cancer-related cause of death after lung cancer in men and breast cancer in women. In 2009, CRC caused an estimated 49,920 cancer deaths in the U.S. American Cancer Society .: Cancer Facts and Figures 2009. (Atlanta, Ga: American Cancer Society, 2009. Also available online 10. Last accessed January 6, 2010) and approximately 251,000 in Europe in 2008; (http://www.who.int/healthinfo/global_burden_disease/projections/en/index.html). Of the newly diagnosed cases, 15-25% correspond to patients who present metastatic disease at the time of diagnosis (Kindler and Shulman, 2001) and up to 50% of all patients finally present metastatic disease (Kindler and Shulman, 2001; McLeod et al, 2000). In general, CRC is curable if the diagnosis is made early and is localized to the intestinal mucosa, with a 5-year survival of 93% (Pazdur et al, 1999). However, the 5-year survival rate falls to 67% after adjacent organ and lymph node involvement and is only 8% in patients with disseminated metastatic disease (Pazdur et al, 1999; Kindler and Shulman, 2001).

Analyzing the situation in Spain in more detail, according to data from the National Statistics Institute (INE, 2006 data published in January 2008), the second most significant type of cancer in men was colon cancer with 5,642 deaths. This tumor accounted for 4,284 deaths in women (http://www.ine.es/jaxi/tabla.do http://www.ine.es/prensa/np490.pdf).

Taking SEOM as a source, in Spain more than 25,000 new cases of CRC are diagnosed each year (15% of the incidence of all tumors). In addition, it is the second leading cause of death from cancer in our country, after lung cancer, with more than 13,000 deaths per year. A figure that is well above the data for deaths from AIDS, with more than 1,300 a year, and from traffic accidents, with more than 4,000 *(http://www.seom.org/seomcms/images/stories/recursos/home/2009/Dossier_Prensa.pdf).*

Colorectal Cancer Treatment

Historically, the median survival of patients with metastatic disease has been 11-13 months with modulation with fluoropyrimidine, 5-fluorouracil and leucovorin (LV) (Advanced Colorectal Cancer Meta-Analysis Project 1992). The introduction of oxaliplatin and irinotecan in advanced colorectal cancer chemotherapy has increased the frequency and magnitude of clinical response compared to that achieved with 5-FU / LV alone, and has increased progression-free survival and overall survival. Research is currently underway to determine how this systemic therapy can be optimized.

Irinotecan, a specific DNA topoisomerase I inhibitor, has shown significant activity as a single agent in the treatment of patients with CRC refractory to 5-FU (Rougier et al 1998; Cunningham et al 1998). Furthermore, the addition of irinotecan to 5-FU / LV combination therapy (FOLFIRI regimen) produced a significant improvement over 5-FU / LV alone in overall survival, response rate, and time to progression in the treatment of patients with previously untreated mCRC (Douillard et al, 2000).

Oxaliplatin, a platinum analog, forms cross-linked adducts and blocks deoxyribonucleic acid replication. Oxaliplatin has been shown to be effective and well tolerated when given with leucovorin bolus and infusion (FOLFOX regimen), although neutropenia and sensory neuropathies

occur more frequently than when 5-FU and LV are given alone (Maindrault-Goebel et al, 1999; de Gramont et al, 2000; Rothenberg et al, 2003; Goldberg RM et al, 2004; Tournigand et al, 2004).

The last few years have been accompanied by advances in the treatment of mCRC that have improved the life expectancy of patients.

Among the latest additions to mCRC therapy are biological therapies or targeted therapies, of which we could highlight drugs directed against the vascular growth factor receptor (VEGF) and those directed against the epidermal growth factor receptor (EGFR). ).

Target biological agents, specifically designed to inhibit the biochemical processes of carcinogenesis, have been shown to be effective in treating mCRC. Cetuximab (Erbitux®), a chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFr), is cleared by the FDA for use in combination with irinotecan for the treatment of patients with mCRC who have tumors that express EGFr that are resistant to irinotecan-based treatment or as monotherapy in irinotecan-intolerant patients with tumors that express EGFr (Baselga and Mendelson, 1994; Herbst et al, 2002; Cunningham et al, 2004; Saltz et al, 2004). Within the European Union, the authorization allows patients with metastatic colorectal cancer to be treated with non-mutated KRAS with expression of the epidermal growth factor receptor (EGFr) in combination with chemotherapy or as monotherapy in patients whose treatment based on irinotecan and oxaliplatin failed and they do not tolerate irinotecan (Erbitux® SmPC, 2009).

Another selective product is bevacizumab (Avastin®), which binds and inhibits endothelial growth factor A (VEGF-A), a protein that plays a crucial role in tumor angiogenesis. Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum (Avastin® SmPC, 2009).

There are two monoclonal antibodies directed against EGFR: panitumumab and cetuximab.

Panitumumab currently has an indication “as monotherapy for the treatment of patients with metastatic colorectal carcinoma expressing EGFR with wild-type KRAS, after the failure of chemotherapy regimens containing fluoropyrimidine, oxaliplatin and irinotecan (Vectibix SmPC ) ".

The monoclonal antibody cetuximab has, since July 2008, in light of the information provided to the health authorities, authorization by the EMEA to be used in the first line in patients with mCRC who meet the requirements reflected in the approved indication (Technical Sheet by Erbitux)

Cetuximab is indicated for the treatment of patients with mCRC, with expression of the epidermal growth factor receptor (EFGR), with a native-type KRAS gene:
in combination with chemotherapy,
as monotherapy in those patients in whom treatment with oxaliplatin and irinotecan has failed and who cannot tolerate irinotecan (Erbitux SmPC).

Thus, the current indication for the first line of treatment in patients with mCRC with expression of the epidermal growth factor receptor (EFGR), with the KRAS gene of the non-mutated type, included in the technical data sheet, is achieved after a complete clinical development of the drug. , culminating in the CRYSTAL and OPUS trials, clear exponents of the use of cetuximab in regimens with irinotecan and oxaliplatin, in the first line of treatment, common guidelines in daily clinical practice.

CRYSTAL study

The CRYSTAL study was designed to assess the efficacy of adding cetuximab to FOLFIRI in the first-line treatment of metastatic colorectal cancer. This is a phase III study comparing FOLFIRI vs. FOLFIRI + cetuximab. The sample size was 1198 patients, randomized 1: 1 by region of origin and ECOG status. Its design considered progression-free survival as the primary endpoint and overall survival, response, and safety as secondary endpoints. The efficacy analysis according to KRAS status was retrospective.

At the last ECCO / ESMO congress (Berlin, 2009), updated survival data were presented for these native KRAS patients, treated with the combination of FOLFIRI-cetuximab, after a longer follow-up time and a greater number of KRAS determinations. The number of patients with KRAS status determination increased from 45% to 89% in this update. In these patients, a significant increase was demonstrated both in the OR (57.3 vs 39.7, $p < 0.0001$), as well as in the SPL (9.9 vs 8.4 months, $p = 0.012$) and the overall survival, until now not reached (23.5 vs 20 months , $p = 0.0094$, HR: 0.8, 95% CI: 0.67-0.95). (Lang I, Könhe CH, Folprecht G et al. Cetuximab plus Folfiri in 1st line treatment of mCCR: quality of life analysis of patients with KRAS WT tumors in Crystal trial. Presented at: ASCO gastrointestinal Cancers Symposium. January 2010 (Abstract 281)

In a recent update of the data at the ASCO GI 2010 congress, the results are reported after determining the KRAS status of 89% of the sample (in the original publication it was only 45%). A benefit of the addition of cetuximab to FOLFIRI in KRAS WT patients was confirmed in terms of progression-free survival (HR 0.70; 95% CI 0.56-0.87), overall survival (HR 0.80; 95% CI 0.67-0.95) and response ( OR 2.07 95% CI 1.52-2.83). (Van Cutsem E, et al. ASCO GI Congress 2010. Abstract No: 281.)

These data were presented together with their update according to the mutational status of KRAS and BRAF (determined in 83% of patients), in the past ASCO GI (Van Cutsem E, Lang I, Folprecht G, et al. Cetuximab plus Folfiri in the treatment of metastatic colorectal cancer (mCRC): the influence of KRAS and BRAF biomarkers on outcome: updated data from the Crystal trial. Presented at: ASCO gastrointestinal Cancers Symposium. January 2010 (Abstract 281), maintaining superiority in terms efficacy of the combination of QT with cetuximab in native KRAS patients. These results were superior in patients with native KRAS and native BRAF, and the presence of mutated BRAF worsened the results, regardless of the treatment used, the authors concluding that the BRAF mutation is a negative prognostic factor in mCRC.

OPUS 20 study

The OPUS 20 study is a randomized phase II trial, comparing FOLFOX vs. FOLFOX + cetuximab in the first line of metastatic colorectal cancer treatment. The sample size was 292 patients, randomized 1: 1 by ECOG status.
Its design considered superiority in the percentage of response in the experimental arm as a primary objective. The efficacy analysis according to KRAS status was, as in CRYSTAL, retrospective.

In the past ECCO / ESMO (Berlin, 2009), updated efficacy data of the combination of FOLFOX-4-cetuximab in patients with native KRAS was presented, after increasing the number of patients in whom the determination of mutational status was performed. (93.5%) (Bokemeyer C, Bondarenko I, Hartmenn JT, et al. Overall survival of patients with KRAS wild-type tumors treated

with FOLFOX-4 ± cetuximab as 1st line treatment of metastatic colorectal cancer: the OPUS study. Updated information presented at the 15th Congress of the European cancer Oragnization / 34th Congress of the European Society of Medical Oncology. Abstr. 6079). In these patients, the median overall survival was 22.8 months in the cetuximab arm, compared to 18.5 months in the QT alone arm (p = 0.38). The updated global response data was 57.3% in the patients treated with cetuximab vs 34% in the other arm (p = 0.027) and progression-free survival was 8.3 months in the arm that associated cetuximab, maintaining 7.2 months achieved in patients treated only with CT (HR = 0.57, 95% CI (0.38-0.86), p = 0.0064), which represents a 43% reduction in the risk of disease progression.

In a recent update of the data at the 2010 ASCO GI symposium, the results are reported reaffirming the efficacy of the combination of cetuximab and FOLFOX-4 in patients with native KRAS, after determining the KRAS status of 93.5% of the sample (in the original publication was made of 69.1%). The OPUS study confirms, once again, a benefit of the addition of cetuximab to FOLFOX in KRAS WT patients in terms of progression-free survival (HR 0.57; 95% CI 0.38-0.86) and response (OR 2.55 95% CI 1.38 -4.72). No benefit in overall survival was shown. (Bokemeyer C, Bondarenko I, Hatmann JT, De Braud FG, et al. Biomarkers predictive for outcome in patients with mCRC tretaed with first-line FOLFOX-4 plus or minus cetuximab: Updated data from the OPUS study. Presented at: ASCO gastrointestinal Cancers Symposium. January 2010 (Abstract 428).

A meta-analysis performed with individual data from both studies (n = 845, absence of heterogeneity for progression-free survival, overall survival, and response) was also reported at the 2010 ASCO GI symposium, confirming the benefit of adding cetuximab first-line to KRAS WT patients both in terms of progression-free survival (HR 0.66, 95% CI 0.55-0.80), overall survival (HR 0.81, 95% CI 0.69-0.94) and response percentage (OR 0.81, 95% CI 0.69-0.94 ) (Koehne C, et al. ASCO GI Congress 2010. Abstract No: 406).

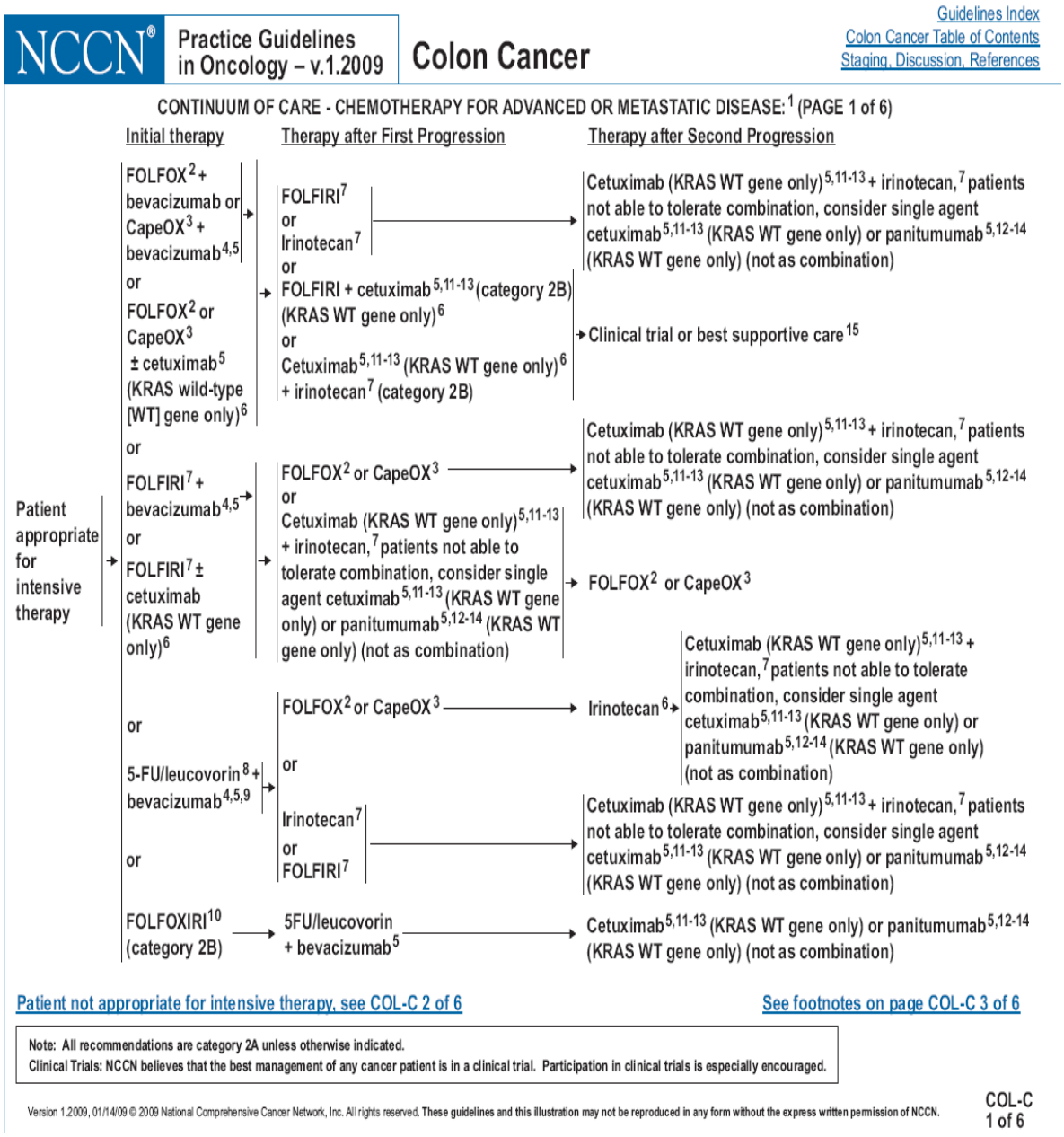
At these same congresses, a meta-analysis has been presented that collects the efficacy data of the addition of cetuximab to the 1st-line QT of mCRC in the CRYSTAL and OPUS studies (Van Cutsem E, Rougier P, Köhne C, et al. . A meta-analysis of the Crystal and Opus trials. Eur J Cancer Suppl. 2009; 7: 354. Updated information presented at the 15th Congress of the European cancer Oragnization / 34th Congress of the European Society of Medical Oncology. Abstr. 6077) . This study collected independent data from a total of 845 patients with mCRC and native KRAS (666 from the Crystal study and 179 from the Opus). This analysis showed that adding cetuximab provides a clear benefit in the global response, doubling the possibility of obtaining a response, and an increase in PFS of patients with native KRAS: it reduces the risk of disease progression by 34% (HR : 0.66; p <0.001). Furthermore, it also demonstrated a significant increase in survival in native KRAS patients receiving cetuximab (HR: 0.81; p = 0.0062) (Table 6) (Kohne C, Rougier P, Stroh C, et al. Cetuximab with chemotherapy as first-line treatment for metastatic mCRC: A meta-analysis of the CRYSTAL and OPUS studies according to KRAS and BRAF mutation status. Presented at: ASCO gastrointestinal Cancers Symposium. January 2010 (Abstract 406).

| **HR/odds ratio** | **95% CI** | **p value** | **Heterogeneity p value** |
|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **OS** | 0.81 | 0.69-0.94 | 0.0062 | 0.6696 |
| **PFS** | 0.66 | 0.55-0.80 | <0.0001 | 0.3332 |
| **ORR** | 2.16 | 1.64-2.86 | <0.0001 | 0.5568 |

*Conclusion*

*The NCCN 21 guidelines propose the use of cetuximab in combination with chemotherapy drugs in the first line in patients with mCRC and Kras mutational status not mutated.*



### *4.3. Previous experience and justification for the biweekly cetuximab regimen*

The standard administration schedule for cetuximab involves a weekly infusion of the drug. The biweekly form of administration (ie every 14 days) has two advantages: it is more comfortable for patients and represents a saving of resources for health systems.
However, this benefit would be greater in the case of treatment of CRC with cetuximab, because most chemotherapy regimens with which cetuximab is combined are administered every 14 days.

This possibility has been studied in clinical trials based on a previous demonstration that the pharmacokinetics and pharmacodynamics of the weekly and biweekly regimens are equivalent. Phase II clinical trials of combination of cetuximab with chemotherapy provide data that support the hypothesis that the toxicity and efficacy of the biweekly regimen is similar to the weekly regimen.

The evidence behind the decision to use the biweekly cetuximab regimen in this trial is detailed below:
A prospective, multicenter, uncontrolled clinical trial presented at the ASCO 2008 GI Symposium, evaluating the safety profile of 70 patients treated with irinotecan plus cetuximab 500 mg / m2 every 2 weeks. Grade 3 and 4 toxicities included neutropenia (6%), diarrhea (6%), asthenia (7%), and acne-like skin rash (11.4%). The primary endpoint of the study was PFS at 12 weeks. 29 patients were evaluable, and the 12-month PFS rate was 52%. The authors concluded that cetuximab every 2 weeks is as active and as safe an option as standard weekly therapy. (J.M. Roca, V. Alonso, C. Pericay et al. Cetuximab given every 2 weeks plus irinotecan is an active and safe option for previously treated patients with metastatic colorectal cancer. ASCO Gastrointestinal Cancers Symposium 2008; 388).

An exploratory trial of the biweekly treatment of irinotecan and cetuximab in patients with metastatic colorectal cancer who had progressed to at least one prior chemotherapy. In this trial a total of 40 patients were treated with Irinotecan 180 mg / m2 and cetuximab 500 mg / m2 every 2 weeks in 21-day cycles until unacceptable toxicity or disease progression. The overall response rate was 22.5% (2 complete responses and 7 partial responses). The disease control rate was 60%. Time to progression was 3.4 months and overall survival was 8 months. The biweekly regimen proved to be well tolerated. Grade 3 and 4 adverse effects were observed in 12 patients. The results of this study show that the biweekly regimen in terms of toxicity and efficacy is similar to the weekly administration regimen. (Martín-Martorell P, Roselló s, Rodriguez Braun E, Chirivella I, Bosch A, Cervantes A. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008; 99: 455-8).

A single-center clinical trial of 74 refractory metastatic colorectal cancer patients treated with irinotecan and cetuximab 500 mg / m2 every 2 weeks. Duration of treatment, ORR, median time to progression, and median overall survival were 4.3 months, 25%, 5.4 months, and 8.9 months, respectively. Treatment was well tolerated. (Pfeiffer P, Nielsen D, Bjerregaard J, QvortupC, Yilmaz M, Jensen B. Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluoracil. Ann Oncol 2008; 19: 1141-5)

A study has been published retrospectively comparing the efficacy and safety of the administration of cetuximab in association with irinotecan in two treatment schedules, once a week or every two weeks in patients with metastatic colorectal cancer. The clinical data of 50 patients who had received treatment with cetuximab separated into two groups were studied. The patients in the first group (N = 32) had been treated with an initial dose of 400 mg / m2, followed by a weekly infusion of 250 mg / m2 of cetuximab. The patients in the second group (N = 18) had received cetuximab every two weeks at a dose of 500 mg / m2. Tumor response, time to progression, overall survival, and toxicity were compared in both groups. All patients had received irinotecan and 5-fluorouracil and most had previously received oxaliplatin. The median follow-up for all patients was 34.2 months. The rates of time to progression and 7-month overall survival were similar in both groups. Although the result of the trial taking into account the variable "disease control (partial response + stable disease)" was not statistically significant (56.3% of the patients who received cetuximab weekly, compared to 77.8% in the other group (P = 0.21 )), it is important to note that the most relevant adverse event was dermatological toxicity and only one patient in each group had a grade 3 adverse reaction. The results of this study indicate that the efficacy between the weekly and biweekly regimen of cetuximab is similar without increasing toxicity in association with irinotecan. (Mrabti H, De la Fouchardiere C, Desseigne F, Dussart S, Negrier S, Errihani H. Irinotecan associated with cetuximab given every 2 weeks versus cetuximab weekly in metastatic colorectal cancer. J Cancer Res Ther. 2009 Oct-Dec; 5 (4 ): 272-6)

A phase I clinical trial reported that cetuximab 500 mg / m2 administered every 2 weeks exhibits the same pharmacokinetic profile as the approved weekly regimen and that it can be safely administered every 2 weeks at 500 mg / m2 without major differences in pharmacodynamic profiles. Concluding that the biweekly alternative seems to be an adequate alternative to the weekly regimen. (J.Tabernero, A. Cervantes, E. Martinelli et al. Optimal dose of cetuximab (C) given every 2 weeks (q2w): A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly and q2w schedules in patients with metastatic colorectal cancer. Ann Oncol. 2009 Nov 25, J Clin Oncol. 2010 Mar 1; 28 (7): 1181-9.

These publications strongly support the concept of equivalence, in terms of efficacy and toxicity of cetuximab, between the biweekly and weekly form of administration of this drug.

After the demonstration of differences in the clinical benefit obtained in treatment with weekly cetuximab, among patients with metastatic CRC, taking into account the KRAS mutational status, a clinical trial with the secondary objective of discerning the toxicity profile is justified. when cetuximab is given biweekly.

### *4.4 Justification of the biomarkers under study*

#### *4.4.1 Role of the IGFR pathway in metastatic colorectal cancer*

IGFR is hyper-expressed in CRC. However, no IGFR amplification or mutations have been found in CCR, so it is likely that IGFR transcription activation mechanisms are involved in tumor oncogenesis. IGFR activation leads to phosphorylation of r EGF through the autocrine / paracrine pathway through a metalloproteinase cleavage mechanism of different EGF-like ligands such as heparin-binding EGF, ampheregulin, or tumor necrosis factor alpha (Roudabush et al. al., 2000; El-Shewy et al., 2004).

### *4.4.2 MMP-7 and its relationship with the IGF system*

MMP-7 is a metalloproteinase secreted in the tumor microenvironment by neoplastic cells that acts, normally promoting invasion, tumor progression and the generation of metastases. This metalloproteinase can degrade proteins of the IGRF pathway with a pro-apoptotic function such as IGFBP-3 (Miyamoto et al., 2004) and also activate EGFr (Tan et al., 2005). EGFr can also stimulate the expression of MMP-7. Several in vitro studies correlate activation of the IGFR pathway with resistance to EGFr inhibitors (Chakravarti et al., 2002; Desbois-Mouthon et al., 2006).

It has been observed in vitro that, in the native cell line HT-29, MMP-7 increases after 48 hours of treatment with oxaliplatin and that the basal levels of MMP-7 in HT-29 cells resistant to oxaliplatin (HT-20 OXL -R) are 4 times higher than in native HT-29 cells (Almendro et al., Plos One 2009). We hypothesized that chemotherapy or hypoxia might increase MMP-7. In fact, under hypoxic conditions, one of the most induced genes was MMP-7 (Burke et al., 2003).
We have observed in untreated colorectal cancer patients that MMP-7 increases with disease progression, and that this increase is associated with a reduction in IGFBP-3 levels (Gallego et al., 2009). In HT-29 OXL-R cells, IGFBP-2 has higher levels compared to native HT-29 cells. This increase in the level of IGFBP-2 can cause apoptosis due to the down regulation of pIGF-1R and pAKT, although this will not be the case in HT-29-R cells that express the double positivity condition (pIGF-1R + and MMP- 7 +). Recently, this resistant phenotype related to increased IGF-1R phosphorylation has been reported by Dallas et al. (2009). We propose that after treatment with OXL, IGFBP induces apoptosis by inhibiting phosphorylation of pIGF-1R in HT-29 cell lines but not in HT-29R, by constitutive activation of MMP-7.

In the clinical context, our group retrospectively investigated the role of IGFRp and MMP-7 in metastases or primary CRC in a group of patients with advanced colorectal cancer treated with cetuximab or panitumumab as second or third line treatment (Horndler et al. al., 2009). A total of 104 patients with available tissue from 168 patients were taken to analyze the mutational status of RAS and BRAF and the expression of MMP-7 and IGFRp. There were no significant differences in response rate (18.8% vs. 15%), PFS (3.3 vs. 3 m), and OS (7.76 vs. 7 m) between the total and selected cohorts. Expression of MMP-7 and IGFRp was observed in 49% and 52% of patients, respectively. Co-expression of MMP-7 and IGFRp (double positive group [IGFRp + / MMP-7 +]) was observed in 27/104 patients (26%) and in 15/71 patients (24%) in patients with RAS and BRAF not mutated. There was no correlation between RAS and BRAF mutational status and the double positive group (IGFRp + / MMP-7 +) ($p = 0.52$). In the subgroup of patients with RAS and non-mutated BRAF, the group with double positivity (IGFRp + / MMP-7 +) presented a lower response than patients without double positivity ($p = 0.002$) and showed a trend towards a disappointing PFS of 91 days versus 121 days ($p = 0.09$) and a poor OS of 196 days (95% CI: 175-215) versus 294 days (95% CI: 182-344) ($p = 0.002$).

### *4.4.3 BRAF*

Different publications have established the prognostic and predictive role of the BRAF mutation in metastatic colon cancer. The BRAF mutation is present in 5 to 8% of cases. In the OPUS study (discussed above), a retrospective analysis was made of the prognostic and predictive value of this mutation in the patients included in the study. The percentage of patients with mutated BRAF was 7.9%, and this mutation was associated with both overall survival (HR 1.82, 95% CI 1.36-2.43) but not with progression-free survival (HR 1.14, 95% CI 0.86-1.52). . There are other studies, such as

those of Di Nicolantonio et al. (JCO 2008) and Laurent-Puig et al. (JCO 2009) who also evaluate the prognostic and predictive role of BRAF. In both studies, the BRAF mutation was associated with poorer overall survival and worse progression-free survival. Own data (under review, pending publication) confirm these results. The interest of studying this marker, rather than identifying it as a new prognostic marker, lies in establishing its magnitude in the context of other prognostic markers (creation of a score), as proposed in this protocol.

#### *4.4.4 PTEN*

PTEN, like BRAF, is another component of the MAPK signaling pathway and therefore its mutational status could affect the efficacy of cetuximab. In the Laurent-Puig study discussed above (JCO 2009) they also evaluate this marker. PTEN expression was absent in 19.9% of KRAS WT patients and was associated with both progression-free survival and overall survival. Similarly, another study (Loupakis et al. JCO 2009) evaluated the predictive role of loss of PTEN expression in metastases in patients with colorectal cancer in progression to irinotecan treated with irinotecan plus cetuximab. In this study, the loss of PTEN expression in metastases was shown to be associated with worse progression-free survival ($p = 0.005$).

For all this, we consider that the expression of PTEN, together with BRAF, is another of the markers that we must include in the characterization of the MAPK pathway in this protocol.

### *4.5 Rationale for this trial*

Advanced and / or metastatic colorectal cancer (CCRA) is a heterogeneous disease and the classification of patients is currently poor. Approximately twenty percent of patients have favorable stages (less than 4 nodules in the liver and less than 5 cm) and are suitable for local treatments (surgery or local ablative therapies). Additionally, 10-15% of patients have a poor functional status (ECOG> 2) or are impaired due to geriatric syndromes and / or co-morbidity with diseases that oppose any strategy other than the best supportive therapy. . The rest of the patients (suitable patients not suitable for radical surgery) constitute the population of patients treated with palliative therapies. Despite this, not all patients have the same prognosis. Patients with ECOG 0.1 and LDH levels <ULN (intermediate-risk patients) have better PFS and OS regardless of therapy in all randomized clinical trials (de Gramont et al, JCO 2000; Douillard et al, Lancet 2000; Koopman et al, 2007).

The CRYSTAL study shows a benefit in PFS (1.5 months) in non-mutated KRAS from FOLFIRI plus cetuximab compared to FOLFIRI alone. Currently, the selection of patients for treatment with cetuximab is based on the KRAS mutational status, which allows selecting those patients who will not respond to therapy. Other activity markers should be evaluated.

PTEN
The cytoplasmic expression of PTEN is inversely associated with PFS in colorectal cancer. There are two main retrospective studies evaluating PTEN expression in patients treated with cetuximanb. Prospective validation of this marker has not yet been developed.

Clinical Hypothesis

Our hypothesis is that the proposed markers will make it possible to select those patients who will benefit the most from biweekly cetuximab treatment.

## *4.6 OBJECTIVES*

### *4.6.1 Principal Objective*

Validation of the biomarkers BRAF, IGF1P / MMp7 (DP) and PI3K-PTEN to predict PFS in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS treated with standard chemotherapy plus biweekly cetuximab as first-line therapy.
To identify new biomarkers that can predict progression-free survival (PFS) in non-mutated KRAS patients treated with biweekly chemotherapy (QT) and cetuximab in first-line therapy.
The need to identify additional biomarkers of cetuximab efficacy stems from the small predictive value of the current classification, based on KRAS mutational status, of the efficacy of biweekly cetuximab administration in the group of patients with the disease under study.
The proposed biomarkers are:
1 BRAF mutations
2.IGF-1Rp / MMP-7 (DP)
3.PIK3CA-PTEN.
Identifying additional factors that determine the efficacy of biweekly cetuximab will provide the scientific community with additional stratification factors for clinical trial design and better patient selection for biweekly cetuximab treatment.

### *4.6.2 Secondary Objectives*

Secondary biological markers (MMP-7, IGF-1 and IGFBP3) will be analyzed in serum and tumor tissue to predict acquired resistance.
SG based on proposed classification
Objective response according to RECIST 1.1 (E.J. Cáncer 2009; 228-47)
Describe the safety profile of the Cetuximab 500 mg / m2 every 2 weeks administration regimen in the first-line setting including the incidence of AE and significant changes in laboratory parameters.

To assess the objective response rate (ORR) and duration of response (RD) and overall survival (OS) in subjects treated with biweekly cetuximab in combination with FOLFOX6 (m) or FOLFIRI (m) as a first-line chemotherapy regimen. for subjects with metastatic colorectal cancer with non-mutated KRAS, according to the expression of the different proposed biomarkers.

# 5. EXPERIMENTAL PLAN

## *5.1 Study Design*

Single-arm, multicenter, and prospective phase II clinical trial for validation of biomarkers in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS gene treated with chemotherapy plus biweekly cetuximab as first-line therapy. Patients with non-mutated CCRAyM and KRAS will be eligible.

Patients will be recruited over a 24-month period.

Before inclusion in the study and to confirm eligibility, the investigator or designee will send a sample of the primary tumor to the CUN, which will centrally review the status of KRAS (if the patient already has a prior determination of the status of the KRAS gene, it can be included in the assay without the need to re-determine K-RAS). At the same time, the investigator or designee will review existing radiological images in addition to any other relevant clinical documents (reports, notes, etc.) to confirm that the subject has previously untreated advanced and / or metastatic colorectal cancer.

The proposed biomarkers will be measured at the beginning of the study. Investigators can treat patients with CCRAyM and non-mutated KRAS with biweekly FOLFOX6 (m) or FOLFIRI (m) + cetuximab. Other investigative agents will be excluded.

FOLFIRI (m) / FOLFOX6 (m) will be administered once every 2 weeks until 6 months of treatment, disease progression (PE), or unacceptable toxicity. Cetuximab will be administered every 2 weeks as stipulated in this protocol until disease progression. If patients do not show progression after 6 months of treatment with FOLFIRI (m) and FOLFOX6 (m), they will continue to receive biweekly cetuximab as monotherapy until progression.

Subjects who stop receiving FOLFOX6 (m) / FOLFIRI (m), for example due to toxicity, may receive biweekly cetuximab as monotherapy until disease progression. Following discontinuation of biweekly cetuximab, the treatment period will end and subjects will attend a follow-up safety visit 30 ± 3 days later.
Throughout the trial, subjects will be assessed for tumor response using Response Assessment Criteria for Solid Tumors (RECIST 1.1). The tumor response of the subjects will be evaluated by CT (helical or conventional) thoracic and abdominal performed in the baseline phase and every 12 weeks (three months) until the progression of the disease. In subjects with symptoms that indicate disease progression, tumor response should be assessed at the time of symptoms.

Serum biomarker measurements will be performed: until disease progression is documented (every 12 weeks +/- 1 week).

All subjects who discontinue treatment before disease progression (eg, due to unacceptable toxicities) will be followed for PFS (eg, radiographic tumor evaluations) every 12 weeks until progression of the disease or the end of the study (unless the reason for abandoning the study is the total withdrawal of consent).

Once the patient has progressed, the long-term follow-up period of 24 months will begin from the date of progression (every 3 months).

K-RAS, in patients who do not have a previous determination, and other markers of tumor tissue will be measured at the University Clinic of Navarra (CUN) and the markers of the blood samples will be measured at the Hospital Clínic de Barcelona (HCB) .
Biomarkers will be measured prior to patient enrollment. In addition, blood samples will be collected every 3 months until disease progression.

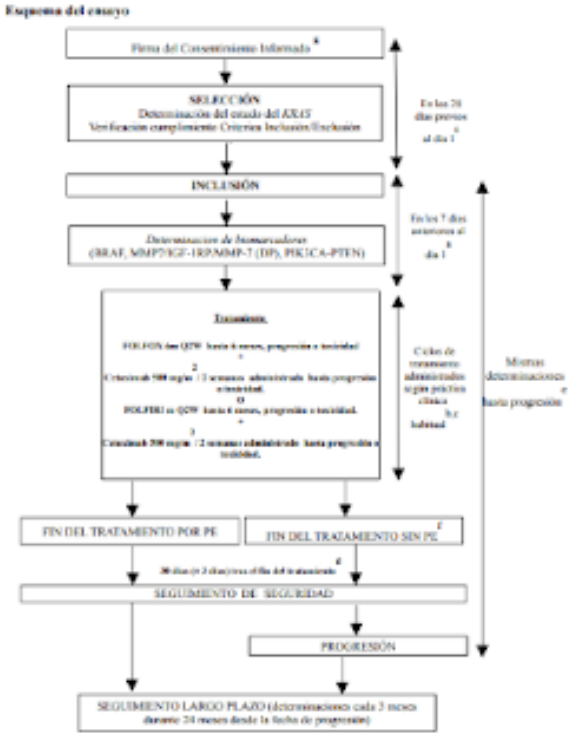
The proposed biomarkers (BRAF, MMP7 / IGF-1RP / MMP-7 (DP), PIK3CA-PTEN) will be used as independent variables in a multivariate model containing other established prognostic variables to predict PFS. A classification will be constructed based on the ability to predict the response of the biomarkers.

5.1.1 Premature withdrawal of treatment:

Treatment will be interrupted in case of:
Withdrawal of consent from the patient
Progressive disease
Intolerable toxicity
Investigator's decision based on what he considers best for the patient

Single-arm, multicenter, prospective phase II clinical trial for biomarker validation in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS gene treated with chemotherapy plus biweekly cetuximab as first-line therapy

## Study Schema




a Day 1 = day of the first treatment administration.
b Subjects' tumor response will be assessed every 12 weeks, throughout the trial until PE (per revised RECIST 1.1 criteria) or withdrawal from the study.
c Subsequent cycles could be delayed due to toxicities associated with cetuximab or chemotherapy.
d All subjects who permanently discontinue treatment (discontinuation is considered completion of all treatment) for any reason will undergo a follow-up safety assessment 30 days ± 3 days after the last dose of treatment. After the safety follow-up visit, subjects who have not progressed will be followed up every 12 weeks as defined in the study. Subjects who undergo surgery for metastases should follow the controls every 12 weeks as established in the protocol. In case of progression by RECIST 1.1 criteria ,. Subjects will be monitored for disease status, subsequent cancer treatment, and survival (long-term follow-up).
e All subjects who discontinue treatment prior to disease progression (eg, due to unacceptable toxicities) will be followed up for PFS (eg, radiographic tumor assessments) every 12 weeks until the progression of the disease or the end of the study (unless the reason for abandoning the study was the total withdrawal of consent).
F. The end of treatment is understood to be the last day the patient has received the last drug of the combination under test (FOLFOX6 (m) / FOLFIRI (m) / Cetuximab). The safety visit should be carried out 30 ± 3 days after the end of the treatment, regardless of the cause that caused it. If the patient has not progressed, imaging and biomarker determinations should continue every 12 weeks until progression as specified in this protocol.
g. In order to mobilize any biological sample, the signing of the informed consent will be mandatory. If the patient already has a previous determination of the status of the KRAS gene, he can be included in the test without it being necessary to re-determine the mutational status of K-RAS.

### *5.2 Number of sites*

Approximately 30 centers in Spain will participate (see attached list)

### *5.3 Number of subjects*

The participants in this clinical investigation will be called subjects.
The expected sample size is 170 subjects enrolled to receive chemotherapy. The justification for the sample size can be found in section 10.2.5.

### *5.4 Estimated study duration*

#### 5.4.1 Study duration for the participants

The inclusion period is expected to last approximately 24 months.

Throughout the trial, subjects will be assessed for tumor response using Response Assessment Criteria for Solid Tumors (RECIST 1.1). The tumor response of the subjects will be evaluated by CT (helical or conventional) thoracic and abdominal performed in the baseline phase and every 12 weeks (three months) until the progression of the disease. In subjects with symptoms that indicate disease progression, tumor response should be assessed at the time of symptoms.

To assess overall survival, all patients will be followed up by visits to the center or by telephone contact every 12 weeks ± 4 weeks from the date of progression up to 24 months after inclusion or death of the last subject, which happen first.

Therefore, the estimated maximum duration of the study is about 48 months (4 years).

#### 5.4.2 End of study

Subjects will follow study procedures until the end of the clinical study, death, withdrawal of consent from the study, and / or loss to follow-up. The study will end when the last subject has completed the long-term follow-up period or has died, whichever occurs first.

## 6. SUBJECT ELIGIBILITY

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be included in this study:

### *6.1 Inclusion criteria*

Male or female ≥ 18 years old.
Able to understand, sign and date an informed consent form approved by the CEIC.
Advanced and / or metastatic colorectal cancer confirmed histologically or cytologically by the investigator.
KRAS non-mutated colorectal cancer.
At least 1 unidimensionally measurable lesion> 10 mm with helical CT or> 20 mm with conventional CT according to the revised RECIST 1.1 criteria. (All disease sites should be evaluated ≤ 28 days before the start of treatment).
Patients with the following characteristics will be included:
1. Recurrence after adjuvant treatment +/- radiotherapy with a disease-free interval> 6 months after completion.
2. De novo diagnosis of the disease.
ECOG (Eastern Cooperative Oncology Group) performance status of 0, 1 or 2. (recommended only 0-1)
Life expectancy ≥ 3 months.
Adequate bone marrow function: neutrophils ≥1.5 x 109 / L; platelets ≥ 100 x 109 / L; hemoglobin ≥9 g / dL.
Liver, kidney and metabolic functions as follows:

Adequate liver function: ASAT (SGOT) and ALAT (SGPT) 2.5 x ULN (5 x ULN if there are liver metastases). Total bilirubin <1.5 x ULN. Alkaline phosphatase 2.5 x ULN (5 x ULN in case of liver metastases or 10 x ULN in case of bone metastases).
Renal function, calculated as creatinine clearance or creatinine clearance for 24 hours ≥ 50 mL / min.
Magnesium ≥ ULN, calcium ≥ ULN.

### *6.2 Exclusion criteria*

PS> 2 or elderly patients with frailty criteria, according to the investigator's criteria.
Previous surgery for metastases (liver, lung or other).
Patients who have received previous systemic treatment for metastatic colorectal carcinoma.
Pretreatment with anti-EGFr antibodies (eg, panitumumab) or treatment with small molecule EGFr tyrosine kinase inhibitors (eg, erlotinib) or EGFr signal transduction inhibitors. Subjects who discontinue their first dose of anti-EGFr therapy (panitumumab) due to an infusion reaction may participate in this clinical trial.
Metastases in the brain / central nervous system (exception: subjects who have been treated, have asymptomatic metastases in the central nervous system and have not received steroids for at least 30 days prior to study inclusion).
Previous malignant tumor within the last 5 years, except for a history of basal cell carcinoma of the skin or preinvasive cervical cancer.
Unresolved toxicities from prior systemic treatment that, in the opinion of the investigator, render the patient ineligible for inclusion.
Presence of peripheral neuropathy (grade> 1 of version 3.0 of the common toxicity criteria (CCT)), and of serious wound or ulcer without healing or open bone fracture.

Hormone therapy, immunotherapy, or experimental or approved antibodies / proteins (eg, bevacizumab) ≤ 30 days prior to enrollment.
Significant cardiovascular disease, including unstable angina or myocardial infarction within 12 months prior to the start of study treatment or a history of ventricular arrhythmia.
History of interstitial pneumonitis or pulmonary fibrosis or evidence of interstitial pneumonitis or pulmonary fibrosis on baseline chest CT scan.
Treatment for systemic infection within 14 days prior to the start of study treatment.
Acute or subacute bowel occlusion and / or active inflammatory bowel disease or other bowel disease causing chronic diarrhea (defined as> 4 loose stools per day).
History of Gilbert's syndrome or dihydropyrimidine deficiency.
History of any illness that may increase the risks associated with study participation or may interfere with the interpretation of the study results.
Known positive test for human immunodeficiency virus infection, hepatitis C virus with abnormal liver enzyme values, chronic active hepatitis B infection. Hepatitis C seropositive patients with normal liver enzyme values may be included.
Any concurrent illness that may increase the risk of toxicity.
The subject has a disorder of any kind that compromises their ability to provide written informed consent and / or comply with study procedures
Have received any investigating agent within 30 days prior to listing.
Pregnant or lactating woman, or planning to become pregnant within 6 months after the end of treatment.
Surgery (not including diagnostic biopsy or central venous catheter placement) and / or radiation therapy within 28 days prior to study enrollment.
Woman or man of childbearing potential who does not agree to take adequate contraceptive precautions, that is, to use 2 contraceptive methods together, at least 1 of them barrier (eg, contraceptive pills plus condom) or abstinence during over the course of the study and for 6 months after the last study drug administration for women and 1 month for men.
The subject is unwilling or unable to meet the requirements of the study.
Psychological, family, sociological or geographical conditions that potentially prevent compliance with the study protocol and the follow-up calendar. These conditions should be discussed with the patient before registering for the clinical trial.

### *6.3. Subject inclusions*

Before the subjects can be included in the study, the sponsor needs to have a copy of the written approval of the protocol, the informed consent and the rest of the subject's information and / or inclusion material that may come from the Ethics Committee. Clinical Research Committee / Institutional Review Committee (CEIC / CRI) of the center and the AEMPS Approval.

Any subject who passes the selection period (defined as the moment the subject signs the informed consent) will be registered and will receive a unique identification number of the subject before any study procedure is performed. This number will be used to identify the subject throughout the clinical study and should be used in all study documentation related to that subject.

Study treatment should begin within 28 days of baseline CT.

### *6.4 Treatment assignment*

The selection of treatment between FOLFOX-6 (m) + biweekly cetuximab or FOLFIRI (m) + biweekly cetuximab will be made by the Principal Investigator, according to the usual clinical practice of his center.

After confirmation of eligibility, the center's staff will fax an inclusion request form to the Sponsor (GEMCAD Technical Secretariat [redacted]) in which they must record the treatment chosen by the Principal Investigator for the patient.

The GEMCAD Technical Secretariat will return a communication to the center to confirm that a new patient has been registered in the study.

# 7. TREATMENT PROCEDURES

## *7.1. Dosage, Administration, and Biweekly Cetuximab Schedule*

Cetuximab is commercially available. This drug will be formulated, packaged, labeled and stored according to the procedures indicated by the local manufacturer, the supplier and the center.

As it is a commercialized drug of habitual use in the study pathology, the supply will be carried out through the usual channels of the National Health System, with the prior favorable opinion of the CEIC and the approval of the Center's Directorate.

Cetuximab (Erbitux) should be administered under the supervision of a physician experienced in the use of antineoplastic pharmaceuticals. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.

### 7.1.1. Dosage

Before the first infusion, the patient should be administered an antihistamine and a corticosteroid.

This premedication is recommended for all subsequent infusions.

Cetuximab will be administered every 2 weeks, the dose is 500 mg / m2.

In reference to the dosage or modifications of the recommended dose of concomitantly used chemotherapeutic agents, consult the SmPC of these drugs. They should not be administered until one hour after the end of the cetuximab infusion.
Biweekly cetuximab treatment should be continued until underlying disease progresses.

Once a dose reduction has been made, a dose escalation will not be allowed in subsequent cycles.

In no case can the patient be kept in the study with Oxaliplatin or Irinotecan in monotherapy, or in combination with cetuximab without 5-FU.

7.1.2. Administration

Erbitux 5 mg / ml

Erbitux 5 mg / ml is administered intravenously via an infusion pump, gravity drip or syringe pump (for instructions for use and handling, see section 6.6 product data sheet).
The duration of the cetuximab infusion will be 120 minutes in the first cycle, 90 minutes in the second and 60 minutes from the third and later. The maximum infusion rate should not exceed 10 mg / min.
Prior to all cetuximab infusions, appropriate medication will be administered as a prophylaxis against the onset of acute hypersensitivity reaction. The patient should be given an antihistamine and a corticosteroid.
During the first infusion it is advisable for the doctor to be present or close to the treatment area. Patients will receive treatment in an area of the hospital where resuscitation equipment and other drugs are available for the treatment of acute hypersensitivity reactions, such as adrenaline or steroids. If an allergic reaction occurs to the infusion with cetuximab, the patient will be treated according to the best available medical practice. Patients will be asked to report delayed reactions to their physician immediately. Although it is not necessary to check vital signs, careful observation of the patient (up to one hour after the infusion) is required to monitor the possible appearance of AAs (specifically allergic reactions).

Erbitux can be given by gravity drip, infusion pump, or syringe pump. The infusion must be performed with a separate infusion line, which must be flushed with a sterile 0.9% (9 mg / ml) sodium chloride solution for injection at the end of the infusion.

Erbitux 5 mg / ml is supported

• with polyethylene (PE), ethyl vinyl acetate (EVA) or polyvinyl chloride (PVC) bags,
• with infusion sets made of polyethylene (PE), polyurethane (PUR), ethyl vinyl acetate (EVA), thermoplastic polyolefin (TP) or polyvinyl chloride (PVC),
• with polypropylene (PP) syringes for syringe pump.

Care should be taken to ensure aseptic conditions when preparing the infusion.

Erbitux 5 mg / ml should be prepared as follows:

• For administration with an infusion pump or gravity drip (diluted with sterile sodium chloride 9 mg / ml [0.9%] solution): Take one infusion bag of sodium chloride 9 mg / ml (0.9 %) sterile of the appropriate size. Calculate the required volume of Erbitux. Withdraw the appropriate volume of the sodium chloride solution from the infusion bag, using an appropriate sterile syringe with a suitable needle. Take an appropriate sterile syringe and attach a suitable needle. Withdraw the required volume of Erbitux from one vial. Transfer Erbitux to the prepared infusion bag. Repeat this procedure until the calculated volume is reached.
Connect the infusion line and prime with diluted Erbitux before starting the infusion. Use a gravity drip system or an infusion pump for administration. Set and control the speed as previously explained.

• For administration with an infusion pump or gravity drip (undiluted): Calculate the required volume of Erbitux. Take an appropriate sterile syringe (minimum 50 ml) and attach a suitable needle. Withdraw the required volume of Erbitux from one vial. Transfer Erbitux to an empty sterile

bag or container. Repeat this procedure until the calculated volume is reached. Connect the infusion line and prime with Erbitux before starting the infusion.
Set and control the speed as previously explained.

• For administration with a syringe pump: Calculate the required volume of Erbitux. Take an appropriate sterile syringe and attach a suitable needle. Withdraw the required volume of Erbitux from one vial. Remove the needle and insert the syringe into the syringe pump.
Connect the infusion line to the syringe, set and control the infusion rate as previously explained, and start the infusion after priming the line with Erbitux or sterile sodium chloride 9 mg / ml (0.9%) solution. . If necessary, repeat this procedure until the calculated volume has been infused.

7.1.3. Special populations

To date, only patients with adequate renal and hepatic function have been studied (see section 4.4 product data sheet).
Cetuximab has not been studied in patients with pre-existing haematological disorders (see section 4.4 product data sheet).

No dose adjustment is necessary in the elderly, although the experience in patients aged 75 years and over is limited.

7.1.4 Contraindications

Erbitux is contraindicated in patients with known severe (Grade 3 or 4) hypersensitivity reactions to cetuximab.
Before starting a combination treatment, the contraindications of the concomitantly used chemotherapy agents should be taken into account.

7.1.5. Warnings and precautions

*Respiratory disorders*

*Individual cases of interstitial lung disease have been reported in which the causal relationship with cetuximab is unknown. If interstitial lung disease is diagnosed, cetuximab should be discontinued and the patient treated appropriately.*

*Skin reactions*

*If a patient develops a severe skin reaction (grade ≥ 3; US National Cancer Institute - Common Toxicity Criteria, NCI-CTC, v3.0), cetuximab treatment should be discontinued. Treatment can be resumed only if the reaction subsides to grade 2 (see section 4.8 of the product data sheet).*
*If the severe skin reaction has occurred for the first time, treatment can be resumed without change in dose.*
*If severe skin reactions occur for the second or third time, cetuximab should be stopped again. Treatment can be resumed at a lower dose (400 mg / m² after the second time, and 300 mg / m² after the third time) only if the reaction has subsided to grade 2.*
*If severe skin reactions appear for the fourth time, or they do not subside to grade 2 during treatment interruption, permanent discontinuation of cetuximab treatment is required.*

*Electrolyte disturbances*

*Progressive decreases in serum magnesium levels occur frequently, which can lead to severe hypomagnesemia. Hypomagnesemia is reversible after stopping cetuximab treatment. In addition, hypokalemia may occur as a result of diarrhea.*
*Hypocalcemia can also occur; in particular the frequency of severe hypocalcaemia may be increased when used in combination with platinum-based chemotherapy.*
*Serum electrolyte level determinations should be performed prior to treatment and periodically during treatment with cetuximab. Electrolyte replenishment is recommended as needed.*

*Neutropenia and related infectious complications*

*Patients receiving cetuximab in combination with platinum-based chemotherapy are at increased risk of severe neutropenia, which can lead to later infectious complications such as febrile neutropenia, pneumonia, or sepsis. Close monitoring is recommended in these patients, especially in those with skin lesions, mucositis or diarrhea, which may facilitate the development of infections (see section 4.8 of the product data sheet).*

*Special populations*

*To date, only patients with adequate kidney and liver function (serum creatinine ≤ 1.5 times, transaminases ≤ 5 times and bilirubin ≤ 1.5 times the upper limit of normal) have been studied.*

*Cetuximab has not been studied in patients with one or more of the following laboratory parameters:*

- *hemoglobin <9 g / dl*
- *white blood cell count <3000 / mm³*
- *absolute neutrophil count <1500 / mm³*
- *platelet count <100,000 / mm³*

7.1.6. Interaction with other medicinal products and other forms of interaction

The frequency of severe leukopenia or severe neutropenia may be higher and therefore may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia, and sepsis with combination with platinum-based chemotherapy, compared to chemotherapy based on platinum alone (see section 4.4 of the product data sheet).
The frequency of cardiac ischemia, including myocardial infarction and congestive heart failure, and the frequency of hand-foot syndrome (palmoplantar erythrodysesthesia) were higher with the combination with 5-fluorouracil than with the infusion of 5-fluorouracil alone.

A formal interaction study showed that the pharmacokinetics of cetuximab remain unchanged after co-administration of a single dose of irinotecan (350 mg / m² body surface area). Also, co-administration of cetuximab did not alter the pharmacokinetics of irinotecan.

No other formal interaction studies with cetuximab have been performed in humans.

7.1.7. Pregnancy and breatfeeding

EGFR is involved in the development of the fetus. Limited observations in animals indicate a

placental transfer of cetuximab and other IgG1 antibodies have been shown to cross the placental barrier. Animal data did not reveal indicative evidence of teratogenicity. However, depending on the dose, a higher incidence of abortions was observed (see section 5.3). There are insufficient data in pregnant or lactating women.
It is strongly recommended that cetuximab be administered during pregnancy or in women not using adequate contraception only if the potential benefit to the mother justifies the potential risk to the fetus.
It is recommended that women do not breastfeed their infants during treatment with cetuximab and for 2 months after the last dose, as it is unknown whether cetuximab is excreted in human milk.

7.1.8. Adverse Reactions

See SmPC of the product.

7.1.9. Overdose

Currently there is limited experience with single doses greater than 400 mg / m² of surface area. body or weekly administrations of doses greater than 250 mg / m² of body surface. In clinical trials with doses up to 700 mg / m² administered every 2 weeks, the safety profile was consistent with that described in section 4.8. of the product data sheet.

7.1.10. Pharmaceutical Data

List of excipients

Sodium chloride
Wisteria
Polysorbate 80
Citric acid monohydrate
Sodium hydroxide
Water for injections

Incompatibilities

This medicinal product must not be mixed with others except those mentioned in section 6.6 of the product's technical data sheet. A separate infusion line must be used.

Period of validity

2 years.
The physical and chemical stability of cetuximab 5 mg / ml has been demonstrated during use for 48 hours at 25 ° C, if the solution is prepared as described in section 6.6 of the product data sheet. Cetuximab does not contain any antimicrobial preservatives or bacteriostatic agents. From the point From a microbiological point of view, the drug should be used immediately after opening. But used immediately, storage times and conditions prior to use are responsibility of the user and normally they should not exceed 24 hours at a temperature between 2 and 8ºC, unless the opening has taken place under controlled and validated aseptic conditions.

Special precautions for storage

Store in a refrigerator (2 ° C to 8 ° C). Do not freeze.
For storage conditions after opening, see section "Shelf life"

7.1.11. Cetuximab dose modifications for infusion-related reactions

If an infusion-related reaction occurs, the investigator should institute therapeutic measures corresponding to the best available medical practice. Based on previous experience with infusion-related reactions

**Re-administration of treatment after an infusion-related reaction**

Once the infusion rate of cetuximab has been decreased due to the occurrence of an infusion-related reaction, this decrease will continue during subsequent infusions. If a subject develops a second infusion-related reaction at the slower infusion rate, cetuximab should be permanently discontinued. If at any time a patient experiences a Grade 3 or 4 infusion-related reaction, cetuximab will be withdrawn from treatment. If there is any doubt as to whether a subject's reaction is a grade 1-4 infusion-related reaction, the study coordinator and / or principal investigator should be contacted immediately to discuss and grade.

**Proposal to synchronize cetuximab and chemotherapy in case of delays**

| | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 | Week 10 | Week 11 | Week 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cetuximab (mg/m²) | 500 | -- | 500 | -- | 250 | 250 | 500 | -- | ~~500~~ | 250 | 500 | -- |
| Chemotherapy | dose | -- | dose | -- | ~~dose~~ | ~~dose~~ | dose | -- | dose | -- | dose | -- |

Toxicity requiring delay in chemotherapy

Cutaneous toxicity requiring delay in cetuximab

Whenever chemotherapy is administered, cetuximab will be administered at a dose of 500 mg / m² unless dermal toxicity precludes administration.
Whenever chemotherapy must be delayed, cetuximab will be administered at a dose of 250 mg / m² in order to allow the administration of 500 mg / m² one week later, coinciding with the planned administration of chemotherapy.
Provided that cetuximab has been delayed due to skin toxicity, but chemotherapy is given as planned, resolution of skin toxicity will be verified one week later. If appropriate, cetuximab will be administered at a dose of 250 mg / m² to allow a return to synchronous administration at the time of the next chemotherapy administration. It is recommended to use these same principles in anticipated cases of dose reduction of cetuximab.

Cetuximab dose reduction in case of skin reactions:

Other reasons to discontinue cetuximab;
If a patient develops breakthrough illness that, in the opinion of the investigator, requires discontinuation of cetuximab treatment, it should be resolved within a framework that does not require delaying more than one infusion.
After stopping treatment, the patient will continue with cetuximab at the dose she was receiving before treatment.
If treatment must be delayed for a longer period, the patient will discontinue treatment. In special cases with the approval of the coordinator the patient could continue with the treatment.
Treatment with cetuximab will not be interrupted due to delays due to chemotherapy toxicity. In case of chemo delays, the patient will receive cetuximab treatment as planned.

### *7.2. FOLFOX6 (m)*

Drugs in this combination are commercially available. These drugs will be formulated, packaged, labeled and stored according to the procedures indicated by the local manufacturer, the supplier and the center. Consult the product data sheet for information on packaging and formulation, labeling, storage, preparation, supply / return, and counting of the combination.

As they are commercialized drugs of habitual use in the study pathology, the supply will be carried out through the usual channels of the National Health System, with the prior favorable opinion of the CEIC and the approval of the Center's Directorate.

Prior to administration of FOLFOX6 (m) chemotherapy, the investigator or designee will review the subject's hematology and biochemical tests, liver function tests, and the incidence of hematologic or non-hematologic toxicities, and follow the parameters of sections 7.2.2 and 7.2.3 to determine if the treatment is adequate.

#### 7.2.1 Premedication FOLFOX6 (m)

Prior to administration of FOLFOX6 (m), all subjects should receive antiemetic products (eg, oral or IV dexamethasone and 5-hydroxytryptamine3 [5-HT3] receptor antagonists). Antiemetics should be administered on the day of treatment, starting at least 30 minutes before the administration of FOLFOX6 (m). Alternative and additional antiemetics may be used, when clinically indicated, at the discretion of the investigator, or in accordance with standard institutional practice.

7.2.2 FOLFOX6 (m)

Administration of FOLFOX6 (m) chemotherapy will begin on day 1 of each treatment cycle.

The FOLFOX6 (m) regimen will be administered every 2 weeks (+/- 3 days), as follows:

**Table: Scheme FOLFOX6 (m)**

| Drug | Dose | Day | Administration |
|---|---|---|---|
| Oxaliplatin | 85 mg/m$^2$ | 1 | Infusion i.v. of 85 mg / m2 of oxaliplatin in 250-500 ml of D5W and infusion i.v. 400 mg / m2 leucovorin racemate (or 200 mg / m2 l-LV) in D5W, both administered over 120 minutes (± 15 minutes) a at the same time in separate bags using a Yc line |
| Leucovorin | 200 mg/m$^2$ | 1 | |
| Fluorouracil | 400 mg/m$^2$ | 1 | Bolus IV |

aExtension of the oxaliplatin infusion time from 2 to 6 hours is allowed, at the discretion of the investigator, to mitigate acute toxicities. It is not necessary to change the duration of 5-FU and leucovorin infusions.

b At the discretion of the investigator, leucovorin and oxaliplatin may be administered sequentially according to standard treatment and local regulations.

cOxaliplatin is not compatible with normal saline or 5-FU. The infusion line should be thoroughly cleaned with D5W before and after 5-FU administration.

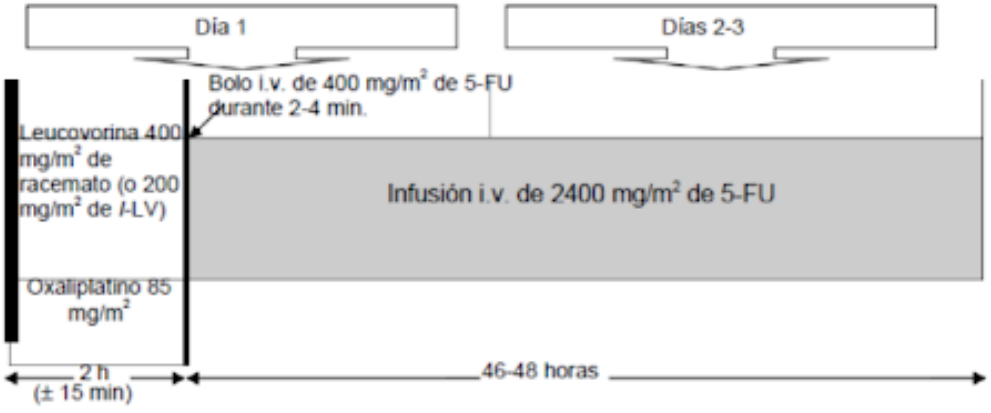



**Figure 2. FOLFOX6 (m) chemotherapy administration schedule**

Every 2 weeks a new cycle of FOLFOX6 (m) treatment will be repeated, although it will not be administered to subjects with ANC <1.5 x 109 cells / L, or if the platelet count is <75 x 109 / L, if the skin toxicity, stomatitis or diarrhea have not recovered to grade ≤ 1, or if fatigue has not recovered to grade ≤ 2. A delay of up to 4 weeks is allowed to start a new course of treatment for resolution of the toxicities. If treatment with one component of the FOLFOX6 (m) regimen (for example, 5-FU / leucovorin or oxaliplatin) is delayed, the other component is also delayed in the same way, so that both therapies can be administered together on day 1 of each. 2 week cycle.

In the event that oxaliplatin administration is interrupted for any reason before 6 months of treatment have elapsed or there is progression of the disease, treatment with 5-FU / leucovorin and cetuximab can continue to be administered once every 14 days ( +/- 3 days) until disease progression or intolerance to study treatment.
In no case can a patient be kept under study with oxaliplatin alone, or in combination with cetuximab.

If the discontinuation of FOLFOX6 (m) chemotherapy is ≤ 6 weeks from the previous cycle, if the subject has recovered from toxicities, as noted above, and if the disease has not progressed, FOLFOX6 chemotherapy should be restarted (m ) with or without cetuximab with the doses specified in Tables 2, 3 and 4. If the interruption of FOLFOX6 (m) chemotherapy is> 6 weeks but the subject has recovered from toxicities and the disease has not progressed, staff The sponsor of the study should review the case together with the investigator to determine if the treatment should be resumed.

7.2.3 Dose levels and dose modification guidelines for the FOLFOX6 (m) regimen

The toxicity of FOLFOX6 (m) in subjects should be closely monitored. Doses of 5-FU and oxaliplatin can be adjusted according to the individual tolerance of each subject. The leucovorin dose will remain fixed at 400 mg / m2 of racemate (d, l-leucovorin) or 200 mg / m2 of l-leucovorin. Table 2 to 4 shows recommended dose levels and guidelines. of dose modification, due to neurological and non-neurological toxicity, of both oxaliplatin and 5-FU.

**Table 3 describes the recommended dose reductions for non-neurologic toxicity.**

**Table 3. Dose reductions of FOLFOX6 (m): non-neurological toxicity**

| | **Initial dose** | **Dose - 1** | **Dose - 2** |
|---|---|---|---|
| Oxaliplatin | 85 mg/m$^2$ | 65 mg/m$^2$ | 50 mg/m$^2$ |
| 5-FU Bolus | 400 mg/m$^2$ | 320 mg/m$^2$ | 240 mg/m$^2$ |
| 5-FU Infusion | 2.400 mg/m$^2$ | 1.900 mg/m$^2$ | 1.500 mg/m$^2$ |

Table 4 below describes the recommended dose modifications at the start of each subsequent therapy cycle. All dose modifications must be based on the worst preceding toxicity.

## Table 4 Dose modifications

**Table 4 Dose modifications**

| **Toxicity**<br>**Grade NCI* (value)** | **Dose level**<br>**for subsequent cycles**<br>**Based on the toxicity of the interval**** | **In the moment of**<br>**retreatment** |
|---|---|---|
| **Absence of toxicity** | Maintain the dose level | Maintain the dose level |
| **Neutropenia (ANC)** | | |
| Grade 1 (ANC < LIN – 1,5 x $10^9$/L) | Maintain the dose level | If ANC <1.5 x 109 / L at the beginning of the cycle, suspend and check weekly, then treat according to the toxicity of the interval. |
| Grade 2 (ANC 1,5 x $10^9$/L - 1,0 x $10^9$/L) | Maintain the dose level | |
| Grade 3 (ANC 1,0 x $10^9$/L – 0,5 x $10^9$/L) | Reduce 1 dose level of 5-FU and OXAL | If ANC <1.5 x 109 / L after 4 weeks, discontinue treatment. |
| Grade 4 (ANC < 0,5 x $10^9$/L) | Reduce 1 dose level of 5-FU and OXAL | |
| **Thrombocytopenia** | | |
| Grade 1 (PLT < LIN - 75,0 x $10^9$/L) | Maintain the dose level | If PLT <75.0 x 109 / L at the beginning of the cycle, suspend and check weekly and then treat according to the toxicity of the interval. |
| Grade 2 (PLT 75,0 x $10^9$/L - 50,0 x $10^9$/L) | Maintain the dose level | |
| Grade 3 (PLT 50,0 x $10^9$/L - 25,0 x $10^9$/L) | Reduce 1 dose level of 5-FU and OXAL | If PLT <75.0 x 109 / L after 4 weeks, discontinue treatment. |
| Grade 4 (PLT < 25,0 x $10^9$/L) | Reduce 1 dose level of 5-FU and OXAL | |
| **Febrile neutropenia** | | |
| ANC < 1,0 x $10^9$/L (neutropenia of grade 3 o 4) y fever ≥ 38,5 ºC | Reduce 1 dose level of 5-FU and OXAL | |

| | | |
|---|---|---|
| **Other hematologic toxicities** | Dose modifications for leukopenia at the start of subsequent cycles of therapy and at the time of retreatment are also based on the NCI toxicity criteria (CTC version 3.0) and are the same as those recommended above for neutropenia. | |
| **Diarrhea** | | |
| Grade 1 | Maintain the dose level | For grade 2 diarrhea at the start of the cycle, suspend and check weekly, then treat according to interval toxicity. |
| Grade 2 | Maintain the dose level | |
| Grade 3 | Reduce 1 dose level of 5-FU and OXAL | If grade 2 diarrhea persists after 4 weeks, discontinue treatment. |
| Grade 4 | Reduce 1 dose level of 5-FU and OXAL. | |
| Other non-hematologic toxicities[1,2] | Dose modifications for other non-hematologic toxicities at the beginning of subsequent therapy cycles and at the time of retreatment are also based on the NCI toxicity criteria (CTC version 3.0) and are the same as those recommended above for diarrhea. | |

The LV dose will not be adjusted due to toxicity. It should remain at 400 mg / m2 racemate (or 200 mg / m2 l-LV) in all cycles. LV should be given just before each 5-FU dose; thus, if 5-FU is delayed, LV will also be delayed.

* Common toxicity criteria from the National Cancer Institute (CTC version 3.0).
** Refers to the starting dose used in the previous cycle.
1 In case of mucositis / stomatitis, reduce only the dose of 5-FU, not that of oxaliplatin.
2 Exceptions: alopecia, fatigue, anorexia, nausea / vomiting if they can be controlled with antiemetics, viral infections.

Table 5 describes the recommended dose modifications for oxaliplatin, based on the duration of neurotoxicity associated with oxaliplatin.

**Table 5. Dose modification rules due to neurotoxicity associated with oxaliplatin**

| **Toxicity (grade)** | **Toxicity duration** | | **Persistente** |
|---|---|---|---|
| | | | **(not resolved between cycles)** |
| | **1 - 7 days** | **> 7 days** | |
| Paresthesias / dysesthesias1 of short duration that resolve and do not interfere with function (grade 1) | No change | No change | No change |

| | | | |
|---|---|---|---|
| Paresthesias / dysesthesias[1] interfering with function but not activities of daily living (ADL) (grade 2) | No change | No change | Dicrease to 65 mg/m$^2$ |
| Paresthesia / dysesthesia[1] with pain or functional impairment that also interferes with ADL (grade 3) | 1st time: dicrease to 65 mg/m$^2$<br>2nd time: dicrease to 40 mg/m$^2$ | DISCONTINUE | DISCONTINUE |
| Persistent paraesthesia / dysesthesia incapacitating or life-threatening (grade 4) | DISCONTINUE | DISCONTINUE | DISCONTINUE |
| Laryngopharyngeal dysesthesias | No change | Increase the duration of the infusion to 6 hours | Increase the duration of the infusion to 6 hours |

[1] May be induced by cold.

Every 2 weeks a new cycle of FOLFOX6 (m) treatment will be repeated, although it will not be administered to subjects with ANC <1.5 x 109 cells / L, or if the platelet count is <75 x 109 / L, if the skin toxicity (not related to cetuximab), stomatitis or diarrhea have not recovered to grade ≤ 1, or if fatigue has not recovered to grade ≤2. A delay of up to 4 weeks is allowed to start a new cycle of treatment for the resolution of toxicities. If treatment with one component of the FOLFOX6 (m) regimen (for example, 5-FU / leucovorin or oxaliplatin) is delayed, the other component is also delayed in the same way, so that both therapies can be administered together on day 1 of each 2 week cycle.

7.2.4 Stopping FOLFOX6 chemotherapy (m)

Subjects will be allowed to receive treatment with FOLFOX6 (m) for up to 6 months or until disease progression, or until unacceptable toxicities and / or consent is withdrawn. If patients do not show progression after 6 months of treatment with FOLFIRI (m) or FOLFOX6 (m), they will continue receiving biweekly cetuximab as monotherapy until progression.

If FOLFOX6 (m) chemotherapy is discontinued before 6 months of treatment or disease progression e.g. due to FOLFOX-6 (m) toxicity, the subject may continue to receive cetuximab monotherapy every 14 days (+/- - 3 days) until you develop disease progression or are unable to tolerate the investigational product.
The disease of all subjects will be reassessed after 12 weeks ± 1 week for the period the patient continues in the trial until progression.

Tumor evaluation will be performed on subjects who have withdrawn from the study for reasons other than radiographically documented disease progression. All these subjects should be monitored for disease progression (revised RECIST 1.1 criteria) every 12 weeks +/- 1 week until disease progression or end of study.

### *7.3 FOLFIRI (m)*

Drugs in this combination are commercially available. These drugs will be formulated, packaged, labeled and stored according to the procedures indicated by the local manufacturer, the supplier and the center. Consult the product data sheet for information on packaging and formulation, labeling, storage, preparation, supply / return, and counting of the combination.

As they are commercialized drugs of habitual use in the study pathology, the supply will be carried out through the usual channels of the National Health System, with the prior favorable opinion of the CEIC and the approval of the Center's Directorate.

Prior to the administration of FOLFIRI (m) chemotherapy, the investigator or his / her designee will analyze the subject's hematology and biochemical tests, liver function tests, and the incidence of hematologic or non-hematologic toxicities, and follow the parameters of sections 7.3.2 and 7.3.3 to determine if the treatment is adequate.

#### 7.3.1 Premedication FOLFIRI (m)

Prior to administration of FOLFIRI (m), all subjects should receive antiemetic products (eg, oral or IV dexamethasone and 5-hydroxytryptamine3 [5-HT3] receptor antagonists). Antiemetics should be administered on the day of treatment, beginning at least 30 minutes before FOLFIRI (m) administration. Alternative and additional antiemetics may be used, when clinically indicated, at the discretion of the investigator, or in accordance with standard institutional practice.

#### 7.3.2 Dose schedule FOLFIRI (m)

Administration of FOLFIRI (m) chemotherapy will begin on day 1 of each treatment cycle.

The FOLFIRI (m) regimen will be administered every 2 weeks (+/- 3 days), as follows:

**Table 5: FOLFIRI regimen (m)**

| Drug | Dose | Days | Administration |
|---|---|---|---|
| Irinotecan | 180 mg/m$^2$ | 1 | IV diluted in 30 - 90 minute infusion |
| Leucovorin | 200 mg/m$^2$ | 1 | IV diluted in 120 IV bolus infusion |
| Fluorouracil | 400 mg/m$^2$ | 1 | IV Bolus |
| Fluorouracil | 2400 mg/m$^2$ | 1 | using an ambulatory pump for a period of 46-48 hours |

FOLFIRI chemotherapy administration schedule (m)

Administration order:
1) Irinotecan and folinic acid in Y administration
2) Fluorouracil using an ambulatory pump for a period of 46-48 hours

A new cycle of FOLFIRI (m) treatment will be repeated every 2 weeks, although it will not be administered to subjects with ANC <1.5 x 109 cells / L, or if the platelet count is <75 x 109 / L, if the skin toxicity, stomatitis or diarrhea have not recovered to grade ≤ 1, or if fatigue has not recovered to grade ≤ 2. A delay of up to 4 weeks is allowed to start a new course of treatment for resolution of the toxicities. If treatment with one component of the FOLFIRI (m) regimen (for example, 5-FU / leucovorin or irinotecan) is delayed, the other component is also delayed in the same way, so that both therapies can be administered together on day 1 of each 2 week cycle.

If irinotecan is discontinued for any reason before 6 months of treatment or disease progression, treatment with 5-FU / leucovorin and cetuximab can be continued once every 14 days ( +/- 3 days) until disease progression or intolerance to study treatment.
In no case can a patient be kept under study with irinotecan alone, or in combination with cetuximab.

If the discontinuation of FOLFIRI chemotherapy (m) is ≤ 6 weeks from the previous cycle, if the subject has recovered from toxicities, as indicated above, and if the disease has not progressed, FOLFIRI chemotherapy should be restarted (m ) with or without cetuximab with the doses specified in Tables 5, 6 and 7. If the interruption of FOLFIRI chemotherapy (m) is> 6 weeks but the subject has recovered from toxicities and the disease has not progressed, staff The promoter of the study should review the case together with the investigator to determine if the treatment should be resumed.

7.3.3 Dose levels and dose modification guidelines for the FOLFIRI regimen (m)

The toxicity of FOLFIRI (m) in subjects should be closely monitored. The doses of 5-FU and irinotecan can be adjusted according to the individual tolerance of each subject. The leucovorin dose will remain fixed at 400 mg / m2 of racemate (d, l-leucovorin) or 200 mg / m2 of l-leucovorin. Tables 5, 6 and 7 show the recommended dose levels and the guidelines for dose modification, due to neurological and non-neurological toxicity, for both irinotecan and 5-FU.

**Table 6 describes the recommended dose reductions for non-neurologic toxicity.**

**Table 6. FOLFIRI dose reductions (m): non-neurological toxicity**

| | **Initial dose** | **Dose - 1** | **Dose - 2** |
|---|---|---|---|
| Irinotecan | 180 mg/m$^2$ | 145 mg/m$^2$ | 116 mg/m$^2$ |

| | | | |
|---|---|---|---|
| 5-FU Bolus | 400 mg/m$^2$ | 320 mg/m$^2$ | 240 mg/m$^2$ |
| 5-FU infusion | 2.400 mg/m$^2$ | 1.900 mg/m$^2$ | 1.500 mg/m$^2$ |

Table 7 below describes the recommended dose modifications at the start of each subsequent therapy cycle. All dose modifications must be based on the worst preceding toxicity.

## Table 7 FOLFIRI dose modifications (m)

**Table 7 FOLFIRI dose modifications (m)**

| **Toxicidad** | **Nivel de dosis** | **En el momento del** |
|---|---|---|
| **Grado NCI* (valor)** | **para los ciclos posteriores** | **retratamiento** |
| | **Basado en la toxicidad del intervalo**** | |
| **Toxicity** | **Dose level** | **In the moment of** |
| **Grade NCI* (value)** | **for subsequent cycles** | **retreatment** |
| | **Based on the toxicity of the interval**** | |
| **Absence of toxicity** | Maintain the dose level | Maintain the dose level |
| **Neutropenia (ANC)** | | |
| Grade 1 (ANC < LIN – 1,5 x $10^9$/L) | Maintain the dose level | If ANC <1.5 x 109 / L at the beginning of the cycle, suspend and check weekly, then treat according to the toxicity of the interval. |
| Grade 2 (ANC 1,5 x $10^9$/L - 1,0 x $10^9$/L) | Maintain the dose level | |
| Grade 3 (ANC 1,0 x $10^9$/L – 0,5 x $10^9$/L) | Reduce 1 dose level of 5-FU and OXAL | If ANC <1.5 x 109 / L after 4 weeks, discontinue treatment. |
| Grade 4 (ANC < 0,5 x $10^9$/L) | Reduce 1 dose level of 5-FU and OXAL | |
| **Thrombocytopenia** | | |
| Grade 1 (PLT < LIN - 75,0 x $10^9$/L) | Maintain the dose level | If PLT <75.0 x 109 / L at the beginning of the cycle, suspend and check weekly and then treat according to the toxicity of the interval. |
| Grade 2 (PLT 75,0 x $10^9$/L - 50,0 x $10^9$/L) | Maintain the dose level | |
| Grade 3 (PLT 50,0 x $10^9$/L - 25,0 x $10^9$/L) | Reduce 1 dose level of 5-FU and OXAL | If PLT <75.0 x 109 / L after 4 weeks, discontinue treatment. |
| Grade 4 (PLT < 25,0 x $10^9$/L) | Reduce 1 dose level of 5-FU and OXAL | |
| **Febrile neutropenia** | | |
| ANC < 1,0 x $10^9$/L (neutropenia of grade | Reduce 1 dose level of 5-FU and OXAL | |

3 o 4) y fever ≥ 38,5 ºC

| | | |
|---|---|---|
| **Other hematologic toxicities** | Dose modifications for leukopenia at the start of subsequent cycles of therapy and at the time of retreatment are also based on the NCI toxicity criteria (CTC version 3.0) and are the same as those recommended above for neutropenia. | |
| **Diarrhea** | | |
| Grade 1 | Maintain the dose level | For grade 2 diarrhea at the start of the cycle, suspend and check weekly, then treat according to interval toxicity. |
| Grade 2 | Maintain the dose level | |
| Grade 3 | Reduce 1 dose level of 5-FU and OXAL | If grade 2 diarrhea persists after 4 weeks, discontinue treatment. |
| Grade 4 | Reduce 1 dose level of 5-FU and OXAL. | |
| Other non-hematologic toxicities[1,2] | Dose modifications for other non-hematologic toxicities at the beginning of subsequent therapy cycles and at the time of retreatment are also based on the NCI toxicity criteria (CTC version 3.0) and are the same as those recommended above for diarrhea. | |

The LV dose will not be adjusted due to toxicity. It should remain at 400 mg / m2 racemate (or 200 mg / m2 l-LV) in all cycles. LV should be given just before each 5-FU dose; thus, if 5-FU is delayed, LV will also be delayed.

* Common toxicity criteria from the National Cancer Institute (CTC version 3.0).
** Refers to the starting dose used in the previous cycle.
1 In case of mucositis / stomatitis, reduce only the dose of 5-FU, not that of oxaliplatin.
2 Exceptions: alopecia, fatigue, anorexia, nausea / vomiting if they can be controlled with antiemetics, viral infections.

## 7.3.4 Interruption of FOLFIRI (m)

Subjects will be allowed to receive treatment with FOLFIRI (m) for up to 6 months of treatment, until disease progression or unacceptable toxicities and / or withdrawal of consent. If patients do not show progression after 6 months of treatment with FOLFIRI (m) or FOLFOX6 (m), they will continue to receive biweekly cetuximab as monotherapy until progression.

If FOLFIRI (m) chemotherapy is discontinued before 6 months of treatment or disease progression, e.g. due to FOLFIRI (m) toxicity, the subject may continue to receive cetuximab monotherapy every 14 days (+/- 3 days) until you develop disease progression or are unable to tolerate the investigational product.
The disease of all subjects will be reassessed after 12 weeks ± 1 week for the period the patient continues in the trial until progression.

Tumor evaluation will be performed on subjects who have withdrawn from the study for reasons other than radiographically documented disease progression. All these subjects should be monitored for disease progression (revised RECIST 1.1 criteria) every 12 weeks +/- 1 week until disease progression or end of study..

### *7.4 Concomitant treatment*

Throughout the study, researchers may prescribe medications or concomitant treatments deemed necessary to provide adequate supportive care, with the exception of those listed in section 7.5.

Concomitant medications will be noted at baseline in the corresponding CRDs and will include all drugs used one month before the start of treatment. For ALL other visits, concomitant medications will be listed ONLY if they are associated with adverse events.

Concomitant medication should be recorded up to 30 days after the last dose of study treatment has ended. Concomitant medication used for medically significant adverse events that are ongoing at the end of study treatment should be followed until the adverse events resolve or are considered stable.

The use of topical, oral or IV antibiotics is allowed. to treat toxicities related to the skin or nails, at the discretion of the investigator; its use will be recorded in the corresponding CRD.
For patients on anticoagulant therapy, close control of coagulation parameters is recommended during the study treatment period.

#### 7.4.1 Growing factors

For low white blood cell counts, granulocyte colony stimulating factor (G-CSF) should be used; however, the routine prophylactic use of G-CSF is not recommended in this study. G-CSF for therapeutic purposes in patients with severe neutropenic complications such as tissue infections, septic syndrome, fungal infections, etc., can be administered at the discretion of the investigator or according to the guideline of the institution. Epoetins may be used at the discretion of the investigator to treat chemotherapy-induced anemia.

### *7.5 Prohibited treatments during the study period*

Subjects should withdraw from the study if they receive during the treatment phase other investigational products, products that act as anti-EGFr other than cetuximab, experimental or approved antitumor treatments (eg bevacizumab), chemotherapy, radiation therapy (except for use for pain control) or systemic steroids (except for use for symptomatic toxicities of the skin or nails that require discontinuation of the dose of cetuximab [see section 7.1.4], use as a premedication of chemotherapy or after chemotherapy to delay chemotherapy-related toxicities or use for an infusion reaction) during the treatment phase.

Rifampizin, phenobarbital, ketoconazole, clarithromycin, erythromycin, HIV protease inhibitors, cyclosporine / tacrolimus, nefazodone, or St. John's wort cannot be co-administered in this study.

Subjects should not be scheduled for any elective surgery (excluding central venous catheter placement) during study participation or up to 7 days after the last study treatment administration (after chemotherapy and / or cetuximab, depending on which is administered last). If a subject

undergoes unplanned surgery during the course of the study, all study treatment should be stopped immediately and the sponsor should be notified as soon as possible. A subject may be allowed to restart study treatment after the sponsor's study team discusses each surgical case with the investigator to determine whether it is appropriate to restart treatment.

## 8. STUDY PROCEDURES

Please refer to the Assessment Schedule (Appendix A) for a description of the procedures to be performed at each visit.
Serious adverse events will be collected as described in section 9.

### *8.1 Selection*

Before carrying out any specific study procedure, informed consent must be obtained, approved by the CEIC, dated and signed. All hematological and biochemical tests, pregnancy tests and carcinoembryonic antigen (CEA) will be analyzed in a local laboratory. Procedures that are part of routine treatment are not considered study specific procedures. Procedures that are part of regular attendance can be used as screening procedures to determine eligibility. Before starting study treatment, all subjects will be evaluated for eligibility. The selection process begins the day the subject signs the informed consent approved by the CEIC and continues until the inclusion of the patient in the trial and subsequent initiation of the study treatment. In this study, only eligible subjects will receive the study treatment.

Before carrying out the study procedures listed below, the KRAS status must be determined by the Central Laboratory of the Navarra University Clinic (CUN) (If the patient already has a prior determination of the status of the KRAS gene, it may be included in the test without the need to re-determine K-RAS).

All subjects must have completed the following procedures in ≤ 28 days (unless otherwise specified) prior to the start of study treatment:
Review of the inclusion and exclusion criteria.
Clinical and medication history
The paraffin-embedded tumor block from both the primary site and the liver metastases must be extracted, prepared and sent to the central laboratory (Clínica Universitaria de Navarra, Pathological Anatomy Service) and the blood samples must be extracted, prepared and sent to the central laboratory ( Hospital Clinic de Barcelona, Pathological Anatomy Service).
These samples will be used to assess KRAS and BRAF mutational status and expression of PTEN, PIK3, MMP-7, IGFRp, IGF-1, IGFBP-3/5, in addition to other possible biomarkers. KRAS mutation status should be performed by an experienced laboratory using a validated method prior to patient enrollment.
Measurements of resting pulse, blood pressure, respiratory rate and temperature.
Weight and height.
Informed consent.
ECOG (Eastern Cooperative Oncology Group) performance status (≤ 7 days before starting study treatment).
Physical examination, laboratory tests (≤ 7 days before the start of study treatment unless otherwise indicated):
Hematological tests: hemoglobin, hematocrit, red cell count (RBC), mean corpuscular volume, platelets, white blood cell count (WBC) and differential WBC (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
Biochemical tests: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN) or urea (depending on the local practice of the center), lactate dehydrogenase (LDH), magnesium, creatinine, albumin, total proteins, total bilirubin, alkaline phosphatase , alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium, phosphorus and uric acid.
Serum biomarker measurements

Serum CEA.
Serum or urine pregnancy test for women of childbearing age (≤72 hours before the start of study treatment).
ECG (all reports will be clinically evaluated by the investigator)
Radiological images of the thorax, abdomen, pelvis, and other locations of the disease by CT (or MRI if clinically indicated); more details in section 8.6.

### *8.2 Inclusion*

Upon confirmation of eligibility, subjects will be enrolled in the study and trial treatment will begin.

### *8.3 Treatment phase*

When all eligibility criteria are met, study treatment should be started as soon as possible. Study day 1 is defined as the day the first dose of treatment is received. One cycle is considered every 14 (± 3) day period plus the time it takes for chemotherapy-related toxicities to resolve.

Cetuximab will be administered at a dose of 500 mg / m2 every 2 weeks on day 1 of each cycle. The concomitant chemotherapeutic agents used should not be administered until one hour after the completion of the cetuximab infusion.

Subjects with unacceptable FOLFOX6 (m) / FOLFIRI (m) -related toxicities may discontinue FOLFOX6 (m) / FOLFIRI (m) treatment and receive biweekly cetuximab as monotherapy. The combined treatment phase runs from enrollment to the decision to discontinue the administration of FOLFOX6 (m) / FOLFIRI (m). The overall treatment period ends when it is decided to discontinue biweekly cetuximab. Evaluations of subjects receiving biweekly cetuximab as monotherapy will be the same as those expected for combination therapy.

During the time of chemotherapy treatment, the following procedures will be performed:
Record of concomitant medication (day 1 of each cycle).
Adverse event log: including toxicities related to skin or nails (day 1 of each cycle).
ECOG (Eastern Cooperative Oncology Group) performance status (day 1 of each cycle).
Physical examination (day 1 of each cycle).
Measurements of resting pulse, respiratory rate, temperature and blood pressure (day 1 of each cycle).
Weight (day 1 of each cycle).
Body Surface Area (SC): will be calculated on Day 1 of Cycle 1 and at the beginning of any cycle during which the subject's weight has changed by 10% from baseline (ie Cycle 1).
Laboratory tests (≤ 48 hours before the start of each cycle). When possible, the same local laboratory should be used throughout the study:
Hematological tests: hemoglobin, hematocrit, red cell count, mean corpuscular volume, platelets, leukocyte count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
Biochemical tests: sodium, potassium, chloride, bicarbonate, BUN or urea (depending on local institution practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorus and uric acid.
Serum CEA (every 8 weeks +/- 1 week).
Radiological images of the chest, abdomen, pelvis and the rest of the disease sites, either by CT or MRI. Disease assessment should be performed every 12 weeks, throughout the trial period until documentation of disease progression.

Serum biomarker measurements: until disease progression is documented (every 12 weeks +/- 1 week).

Treatment will be stopped in the following cases:
Withdrawal of consent from the patient
Progressive disease
Intolerable toxicity
Investigator's decision based on what he considers best for the patient.

### *8.4 Safety follow-up visit*

When a subject definitively discontinues trial treatment, they will undergo a follow-up safety assessment no earlier than 30 ± 3 days after the last dose of study treatment.

The following evaluations will be carried out:
Registration of concomitant drugs.
Adverse event log: including toxicities that are related to the skin or nails.
ECOG performance status.
Physical exploration
Resting pulse, respiratory rate, temperature, and blood pressure.
Weight.
Laboratory tests (where possible the same local laboratory should be used throughout the study):
Hematological tests: hemoglobin, hematocrit, red cell count, mean corpuscular volume, platelets, leukocyte count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
Biochemical tests: sodium, potassium, chloride, bicarbonate, BUN or urea (depending on local institution practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorus and uric acid.
Serum CEA [Note: Serum CEA will only be tested in subjects who have withdrawn from the study for reasons other than disease progression and have not undergone a serum CEA test within 8 weeks +/- 1 week previous].
Radiographic images of the chest, abdomen, pelvis, and other disease sites if the subject withdrew from treatment for reasons other than PE (according to the revised RECIST 1.1 criteria).
Serum biomarker measurements: until disease progression is documented (every 12 weeks +/- 1 week).

All subjects with serious adverse events at the time of the safety follow-up visit will continue with follow-up until resolution of those events..

### *8.5. Follow-up visits from end of treatment without progression to disease progression*

Once the treatment for any cause other than disease progression has been completed, the following procedures will be performed every 12 weeks until disease progression:
ECOG (Eastern Cooperative Oncology Group) performance status.
Physical exploration .
Lab tests. When possible, the same local laboratory should be used throughout the study:
Hematological tests: hemoglobin, hematocrit, red cell count, mean corpuscular volume, platelets, leukocyte count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
Biochemical tests: sodium, potassium, chloride, bicarbonate, BUN or urea (depending on local institution practice), LDH, magnesium, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorus and uric acid.
Serum CEA (every 8 weeks +/- 1 week).

Radiological images of the chest, abdomen, pelvis and the rest of the disease sites, either by CT or MRI. Disease assessment should be performed every 12 weeks, throughout the trial period until documentation of disease progression.
Serum biomarker measurements: until disease progression is documented (every 12 weeks +/- 1 week).

### *8.6 Long-term follow-up visits*

After disease progression, all subjects will be contacted through a clinic visit or by phone (by a member of the center's staff) to assess disease status, subsequent anticancer therapy, and survival after the last drug administration. in study. They will be contacted every 12 weeks ± 4 weeks from the visit (follow-up or security) until 24 months after the last inclusion or death of the last subject, whichever occurs first.

### *8.6 Tumor response evaluation*

During the selection, baseline measurements of the tumor will be performed. Assessments of tumor response will be performed using a revised version of the RECIST 1.1 criteria (Appendix E).

Subjects will be assessed for tumor response every 12 weeks throughout the trial period until disease progression is documented (per the revised RECIST 1.1 criteria). In patients with symptoms suggestive of disease progression, tumor progression should be assessed at the time of symptoms. For subjects in whom disease progression has been determined, the treatment phase of the study will be discontinued and will undergo follow-up safety evaluations 30 days ± 3 days after the last study treatment.

Tumor evaluation will be performed on subjects who have withdrawn from the study for reasons other than radiographically documented disease progression. All these subjects should be followed up for disease progression (revised RECIST 1.1 criteria) every 12 weeks +/- 1 week until disease progression or the end of the study.

At baseline, CT (helical or conventional) with 5-mm slices of the chest, abdomen, and pelvis are required, along with relevant images of all other disease sites. Magnetic resonance imaging (MRI) is not acceptable to evaluate the disease as a single test but can be performed additionally if clinically indicated. If chest CT is normal at baseline, a chest radiograph (CXR) will be performed at each subsequent tumor imaging during the treatment phase. In the event that the chest radiograph is found to be abnormal during the treatment phase, a chest CT will be obtained and this modality should be used to obtain subsequent images of the tumor. If the baseline chest CT is found to be abnormal, a chest CT will be performed during the treatment phase, even if no target lesions have been located on that scan. The same evaluation method and technique should be used to characterize each lesion identified and described at baseline and during follow-up. All radiological evaluations should obtain images of all disease sites identified at baseline, even if they have been chosen by the investigator as non-target lesions.

A change from CT to MRI (or vice versa) of the liver is considered the only acceptable modality change and should not preclude assessment of response if, in the judgment of the center radiologist, there are no significant differences in assessment when changing modalities. This can occur if a subject is medically contraindicated for IV contrast. for CT during the trial. This change would require the prior approval of the developer. CT and MRI are the best and most reproducible methods currently available to measure selected index lesions for response assessment.

Ultrasound should not be used for the evaluation of visceral injuries. However, it is a possible alternative to clinical measurements of palpable superficial lymph nodes, subcutaneous lesions, and thyroid nodules or to confirm the complete disappearance of superficial lesions normally evaluated by clinical examination.

Study treatment (FOLFOX6 (m) / FOLFIRI (m) chemotherapy + biweekly cetuximab) will be discontinued in subjects with PE confirmed by RECIST criteria v.1.1 and will be followed up for safety (after at least 30 days since the last study drug administration).

### *8.7 Withdrawal and replacement of subjects*

#### 8.7.1 Withdrawal of patients

Subjects have the right to withdraw completely or partially from the study at any time and for any reason without prejudice to their future medical assistance by the doctor or the center.

Withdrawal of full consent from a study means that the subject does not wish to receive further investigational treatment, nor does it wish or is unable to continue participating in the study. Any subject can completely withdraw her consent to participate in the study at any time during the study. The investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health. Any subject who completely withdraws their consent to participate in the study will not receive further investigational treatment and / or study observations immediately after the date they request it.

Partial withdrawal of consent means that the subject does not want to continue being treated with the investigational product but still wishes to collaborate by remaining in the study to provide additional data (eg, participating in all subsequent study visits or procedures). Subjects may waive continuing to receive the investigational product at any time during the study. These subjects, in addition to those who have stopped receiving the investigational product for other reasons (eg, decision of the investigator or sponsor) should continue with the study observation program.

Reasons for withdrawal of the investigational product or observation may include:
Withdrawal of consent from the patient
Progressive disease
Intolerable toxicity
Investigator's decision based on what he considers best for the patient

If a subject (or her legally authorized representative) requests or decides to withdraw from the study, every effort should be made to complete and report the observations as widely as possible until the withdrawal date. All information must be included in the corresponding data collection notebooks.

#### 8.7.2 Replacement of subjects

Subjects who withdraw from the study after inclusion will not be substituted. This study will include approximately 170 subjects.

## 9. Collection, registration and notification of security data

### *9.1 Definitions*

9.1.1 Adverse events

In the International Conference on Harmonization (ICH) for Good Clinical Practice, an AE is defined as "any undesirable medical experience in a patient or clinical research subject treated with a pharmaceutical product and that does not necessarily have a causal relationship with it. treatment". (ICH E6: 1.2).

The progression of the disease itself is not considered an adverse event. However, signs and symptoms of disease progression can be recorded as adverse events or serious adverse events. Death due to disease progression during the study should be reported on the death reports page of the data collection notebook, indicating the type of primary tumor as the reason for death.

Worsening of a pre-existing condition (eg, diabetes, migraine headaches, gout) should also be considered an AE if there is an increase in disease severity, frequency, or duration or an association with significantly worse outcomes.

Interventions for pretreatment disorders (eg, elective cosmetic surgery) or medical procedures planned prior to study inclusion are not considered AE.

The investigator is responsible for analyzing laboratory test results and determining whether an abnormal value in a particular study subject represents a change from pre-study values. In general, abnormal laboratory results of no clinical significance (at the discretion of the investigator) should not be recorded as EA; however, changes in laboratory values that require treatment or adjustment from previous treatment will be considered AE.

9.1.2 Serious adverse events

A serious adverse event (SAE) is defined as an AE that
It is mortal.
It is life-threatening (implies an immediate risk of death for the subject).
It requires the hospitalization of the patient or the prolongation of the existing hospitalization.
It results in a persistent or significant disability / incapacity.
It is a congenital anomaly / birth defect.
Another significant medical risk.

A hospitalization that meets the regulatory definition of "severe" is any admission of a patient to the hospital that includes a minimum stay of one night in a healthcare facility. Any AE that does not meet the definitions of severe (eg, accident and emergency department visit, outpatient surgery, or need for urgent study) may be classified as SAE if the investigator considers that it qualifies for "other risk". significant physician ". Examples include allergic bronchospasm, seizures, and blood dyscrasias.

Hospitalization to perform the procedures required by the protocol (or for elective procedures that have been scheduled before inclusion and that are not an exclusion criterion) or the administration of the study treatment is not classified as SAE.

9.1.3 Unexpected adverse event (not listed)

An unexpected AA, the nature or severity of which does not correspond to the information regarding the product.

As all the products administered in this trial are marketed in Spain and are used within the authorized conditions of use, the reference documents to establish the expectancy of adverse events will be the updated technical sheets available at:

https://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm&version=new

In the case of Cetuximab, the information from the latest version of the Investigator's Manual should also be taken into account..

9.1.4 Adverse Drug Reaction (AR) and Serious Adverse Reaction (RAG)

Any harmful and accidental response to a medical product related to any administered dose. The term "response to a drug" means that, at a minimum, a causal relationship between the drug and the adverse event would be a reasonable possibility, that is, the relationship cannot be ruled out.
A severe RA (RAG) is an RA that meets the definition of severe (provided in point 9.1.2).

***9.2 Reporting procedures for all adverse events***

The investigator is responsible for ensuring that all AE (as defined in section 9.1) observed by the investigator or reported by the subjects are correctly recorded in the subjects' medical records, with one exception: those that occur before inclusion and that, furthermore, the researcher does not consider related to the study selection process.

In addition, the investigator is responsible for ensuring that, for subjects included in the study and receiving study treatment, all adverse events recorded in the subjects' medical records (as specified above) are reported in the CRD.

The investigator should record the following attributes of the AE: diagnosis or syndrome (s) of AE (if known; otherwise signs or symptoms), description of the event (with adequate detail for the event), onset dates, and resolution, severity, evaluation of the relationship with the treatment under study and measures taken. The investigator may be required to provide follow-up information, discharge reports, and extracts from medical or CRD records.

If applicable, the relationship of AE to the study treatment will be determined with the following question: "Is there a reasonable possibility that the event may have been caused by the study treatment?" The investigator should answer this question with "Yes" or "No".
If AE has occurred after informed consent but before the start of study treatment, the relationship of AE with the study selection process should be assessed by asking: "Is there a reasonable possibility that the event may have occurred due to the study selection process? " The researcher should answer this question with "yes" or "no". If the answer is yes, it should be recorded which part of the study selection is suspected.

The severity rating scale used in this study is described in Appendix C.
Medically significant AE that the investigator or sponsor considers related to the investigational product will be monitored until resolution or until they are considered stabilized.

It will be up to the investigator's clinical judgment to determine whether an AE is related and severe enough to require removal of the subject from treatment or study. A subject may also voluntarily abandon treatment for what he personally perceives to be intolerable AE. If either of these two situations occurs, the subject should be strongly encouraged to undergo an end-of-study evaluation and remain under medical supervision until symptoms cease or disorder stabilizes.

### *9.3 Reporting procedures for serious adverse events*

The SAEs will be collected and recorded throughout the study period, starting from the signing of the informed consent until 30 days after the last dose of the investigational product or the end of the study (including the follow-up period) if this is produced later. All SAEs recorded in the subjects' medical records (as specified above) must be reported to the study sponsor within 1 business day of discovery or notification of the event. The initial SAE information and all modifications or additions should be recorded in a Serious Adverse Event Data Collection Log and faxed to the sponsor.

SAEs will also be collected and reported within 1 business day of discovery or notification of the event if it appears> 30 days after the last dose of the investigational product or after the end of the study and if it is believed to be possibly related. with the investigational product. In all cases of death, available autopsy reports and relevant medical reports should be faxed to the sponsor. For this reporting process, subject assessments must be made 30 days or more after the last dose of the investigational product has been administered. The determination of whether an adverse event is expected will be based on the contents of the investigator's manual and the technical data sheet for the products marketed. If a subject is permanently withdrawn from the study due to an SAE, this information should be recorded on the initial or follow-up SAE notification form and on the end-of-study CRD.

The researcher must notify: GEMCAD Technical Secretariat.

The telephone and fax number of the contact person:

GEMCAD Technical Secretariat

### *9.4 Notification of adverse events to the regulatory agencies and the CEICs involved.*

The sponsor will assume the responsibility of the adequate communication of the AA to the regulatory authorities.

The sponsor will expeditiously communicate all AAGs that are unexpected and associated with the use of the study treatment (SUSAR) to the researchers, to the clinical research ethics committees (CEIC) in accordance with the regulations in force (unless the CEICs require and document other measures), to the corresponding AEMPS and CCAA.

The sponsor will be responsible for making and submitting to the regulatory authorities and CEIC

the quarterly lists of serious adverse reactions as provided by the R.D. 223/2004 and the GCP.

The sponsor will be responsible for preparing and submitting to the regulatory authorities and CEIC the annual safety reports of the trial, complying with what is specified in R.D. 223/2004 and the GCP. In addition, the sponsor will provide the Cetuximab producing Laboratory with a copy of the annual safety report when it is sent to the competent Health Authorities, as well as to the Clinical Research Ethics Committees.

The sponsor will notify the Clinical Research Ethics Committee and the competent health authorities of any new significant risk to patients as necessary.

The study sponsor is responsible for reporting all suspected serious adverse drug reactions (SARs) that occur in subjects exposed to the cetuximab product to the Merck safety representative in Spain on a regular basis (at least 6 months apart). ). Merck may request tracking information from the developer.

All serious adverse reactions associated or possibly associated with cetuximab and their follow-up reports should be sent to the Merck safety representative in Spain at the same time as they are sent to the regulatory body, the IRC or the CEIC. Within 24 hours of such shipment, a copy of any safety notification concerning the drug cetuximab must be faxed to the regulatory body, CRI or CEIC. The sponsor will be responsible for ensuring that the latest investigator's manual and technical sheet are used as the source document to determine the expected results of an SAE.

# 10. STATISTICAL CONSIDERATIONS

## *10.1 Study design*

Prospective, multicenter, phase II clinical trial designed for the evaluation of predictive tumor biomarkers in patients with advanced and / or metastatic colorectal cancer and non-mutated KRAS tumor treated with biweekly cetuximab as first-line treatment.

The main objective of this study is the validation of the biomarkers BRAF, IGF1P / MMp7 (DP) and PI3K-PTEN to predict PFS in patients with advanced and / or metastatic colorectal cancer with non-mutated KRAS treated with standard chemotherapy plus biweekly cetuximab as first line therapy.

The primary endpoint and secondary efficacy endpoint analysis will be based on the revised RECIST 1.1 criteria (Appendix E) for the intention-to-treat analysis group.

## *10.2. Study variables, subgroups and covariates*

### 10.2.1 Principal endpoint

The primary endpoint is progression-free survival comparing two cohorts, which will be defined according to the classification based on the predictive ability of biomarkers to respond.

Progression-free survival time (PFS): time from the date of inclusion to the date of radiological progression or death (whichever occurs first). Subjects who have not exhibited progression while in the study and have not died while in the study will be censored on the last radiological evaluation date with no evidence of progression. Subjects who have completed study treatment before 48 weeks for any reason should be followed up every 12 weeks as described in this protocol. Subjects who have undergone surgery for metastases will not be censored on the date of surgery, but will be followed as described in the study every 12 weeks until progression is documented. Subjects receiving second-line treatment without documented disease progression will be censored on the date of the last radiological evaluation without progression prior to the change in treatment. If for any reason only the baseline CT was performed (resignation of the subject to continue in the study or loss of follow-up), the case will be censored on day +1 of the inclusion date.

### 10.2.2 Secondary endpoints

Objective response rate (ORR): incidence of a CR or PR according to the revised RECIST 1.1 criteria.

Duration of response (RD): (calculated only for subjects having an objective response) time from first objective response to progression of radiological disease according to the revised RECIST 1.1 criteria. For subjects who present a response and have not had progression, the duration of the response will be censored on the last assessment date of the evaluable disease.

Overall survival (OS): Time elapsed from the date of inclusion to the date of death. For subjects who have not died or who have been lost to follow-up by the data analysis cut-off date, the SG will be censored on the date of the last contact.

Safety: Type, frequency, intensity of adverse events related to the combination treatment.

10.2.3 Subgroup analysis

The intention-to-treat (ITT) analysis group is defined as all subjects who signed the informed consent and who have received the trial treatment, regardless of whether they actually receive any dose of the study treatment. Efficacy presentations will be made to the ITT review group.
A secondary analysis group (analysis group per protocol) will be used to evaluate the efficacy variables in all subjects who signed the informed consent and were included in the study and who did not present significant deviations from the protocol.

10.2.4 Covariates

Efficacy variables can be explored within the following subgroups:
Sex
Age
ECOG performance status
Location of the primary tumor (colon versus rectum)
Number of sites of metastatic disease (1 vs> 1 affected organ)
Baseline LDH concentration
Previous adjuvant chemotherapy (yes or no)
The rest of the subgroup analyzes that are carried out later, if they are carried out, must be notified as such, and the clinical report of the study must state the reason for said analyzes.

10.2.5 Considerations about the sample size

Two groups will be defined based on the classification constructed from the clinical variables and the proposed biomarkers.

The Log-rank method has been used instead of a binomial method for the sample calculation in order to include all the events that occur during follow-up.

A minimum difference of 20% (60 vs. 40%) in PFS is expected at 12 months between groups and with the following assumptions:

Alpha error (bilateral): 5%
Beta error: 20%
Monthly recruitment: 8 patients
Percentage of patients with classification = 0 is 40%

The number of patients required is 155 patients to be recruited in 24 months and a total duration of the trial (recruitment + follow-up) of 28 months for 115 events to occur.

Assuming 10% non-evaluable pts we should include a total of 170 pts.

### *10.3 General considerations*

The primary endpoint and secondary efficacy endpoints will be analyzed using the ITT analysis group and the per-protocol analysis group.

Efficacy analyzes will be based on radiographic images collected during the study and analyzed by the investigator. Any examination that the investigator classifies as not evaluable will be omitted from the analysis (it will be considered as no examination).

For continuous variables, the mean, standard error (for efficacy variables) or standard deviation (for other measurements), median, 25th percentile, 75th percentile, minimum, and maximum will be provided. For discontinuous data, the frequency and percentage distributions will be provided. The two-sided 95% confidence intervals of the Kaplan-Meier quartiles will be calculated using the methods described by Brookmeyer and Crowley (Brookmeyer, 1982). Two-sided 95% confidence intervals for the Kaplan-Meier rates at specific time points will be calculated using the methods described by Collett (Collett, 1992).
Safety data will be analyzed throughout the study.

### *10.4 Analysis of the main variables of the study*

The Cox regression analysis will be performed with the experimental biomarkers and the following prognostic variables (LDH, functional status, age, limited resectable disease (<3 nodules and <5cm). A classification will be performed using the most discriminatory variables. The classification It will be carried out with all the clinical variables of impact in the univariate analysis, including the 4 clinical variables (LDH, functional status, age, limited resectable disease (<3 nodules and <5 cm) and the 3 pathways previously described (BRAF, DP and PTEN). -PI3K) The classification will be carried out with the variables with the greatest impact in the multivariate analysis.
The proposed sample size ensures the construction of a consistent multivariate analysis.

## 11. ETHICAL AND LEGAL CONSIDERATIONS

### *11.1 Ethics Committee*

The study will be carried out in accordance with the principles of the Declaration of Helsinki Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989, 48th General Assembly Somerset West, South Africa, October 1996, 52nd General Assembly, Edinburgh , Scotland, October 2000, Paragraph 29 Clarification Note, added by WMA General Assembly, Washington 2002, Paragraph 30 Clarification Note, added by WMA General Assembly, Tokyo 2004, 59th General Assembly, Seoul, Korea, October 2008 (Annex XIII) and with the standards of Good Clinical Practice (GCP) issued by the working group on Efficacy of Medicinal Substances of the European Economic Community (1990) (CPMP / ICH / 135/95) and the Laws and Regulations in force in Spain.

The Oviedo Convention of April 4, 1997 on human rights and biomedicine, ratified in the BOE in October 1999.

In the regulations for the adequate protection of personal data, according to the provisions of Organic Law 15/1999 on the protection of Personal Data.

The rights and obligations regarding information and clinical documentation, in accordance with the provisions of Law 41/2002, of November 14, basic regulating the autonomy of the patient.

The General Assembly Somerset West, South Africa, October 1996 and the General Assembly Edinburgh, Scotland, October 2000.

Law 14/2007, of July 3, on Biomedical Research.

The researcher will be responsible for preparing the documents to send them to the corresponding Ethics Committee (CEIC) and obtain written approval for the study. Approval will be obtained prior to the start of the study.

Approval for both the protocol and informed consent must specify the approval date, the protocol and version number, or the amendment number.

Any amendment to the protocol after receiving approval from the Ethics Committee must be sent by the researcher to the Ethics Committee for approval. The investigator is also responsible for notifying the ethics committee of any serious deviation from the protocol, or any other matter that implies an added risk for patients.

Any advertisement used to recruit patients for the study must be reviewed and approved by the Sponsor and the ethics committee before use.

### *11.2 Authorities*

The study protocol and / or documents inherent to it will be sent to you before starting the trial, as established by the national authorities.

### *11.3 Protocol Modifications/Deviations*

#### 11.3.1 Protocol Modifications

Protocol amendments, unless necessary to eliminate an immediate hazard to subjects, should only be made with the prior approval of the sponsor. Investigator consensus must be obtained for all amendments made to the protocol and informed consent document. The CEIC and, if applicable, the AEMPS, must be informed of all the amendments and give their approval. The researcher must send a copy of the CEIC approval letter to the sponsor.

Both the sponsor and the researcher reserve the right to interrupt the study, as established in the study contract. The investigator must notify the CEIC of the completion of the study in writing when the study has been completed or prematurely interrupted, and must send a copy of the notification to the sponsor.

Subjects may be eligible to continue treatment with the investigational product by extension of the protocol or as provided by the national regulatory mechanism.

Any modification to this protocol must be agreed by the principal investigator and reviewed by the Sponsor. The written approval of the Ethics Committee and, if applicable, of the AEMPS will be obtained before any modification is implemented.

#### 11.3.2 Protocol deviations

When an emergency occurs that requires a protocol deviation for a patient, the deviation will be performed for that patient only. A decision will be made as soon as it is determined whether the patient (for whom the protocol deviation has been made) is to continue in the study. The patient's medical records will fully describe the deviation from the protocol and will state the reasons for the deviation. In addition, the researcher will notify the Sponsor in writing of said deviation from the protocol.

Once the deviation has been evaluated, if it complies with the stipulations of the local regulations to be communicated, the sponsor will notify CEICs and AEMPS.

Minor deviations from the protocol that are not derived from an emergency will be allowed with the sponsor's approval and should not be communicated to CEICs and AEMPS.

### *11.4 Informed consent*

The investigator must obtain the informed consent of a patient, or their legal representative, before any procedure related to the study in accordance with Good Clinical Practice (GCP) as established in the CFR and ICH guidelines.

Documentation that informed consent was obtained prior to patient entry into the study and informed consent process should be recorded in the original patient documents. The original consent form, signed and dated by the patient and by the person conducting the consent process prior to the patient's entry into the study must be kept in the investigator's study files.

In order to mobilize any biological sample, the signing of the previously informed consent will be mandatory.

### *11.5 Confidentiality*

In order to guarantee the confidentiality of the test data according to the provisions of Organic Law 15/1999 on the protection of Personal Data, only the Test sponsor or personnel designated by him will have access to them for monitoring tasks. / audit, the researcher and his team of collaborators, the Clinical Research Ethics Committee of the corresponding center or the one supervising the trial and the relevant health authorities.

In the aforementioned case of Monitoring / Audits, the researcher must provide direct access to the source documents and data.

The content of the data collection notebooks (CRD) as well as the documents generated during the study will be protected from unauthorized uses by people outside the investigation and, therefore, will be considered strictly confidential and will not be disclosed to third parties except to the specified in the previous section.

### *11.6 Insurance*

All patients in this clinical study are insured through the [redacted], which meets the conditions stipulated by R.D. 223/2004.

## 12. PRACTICAL CONSIDERATIONS

### *12.1 Investigational medicinal product*

TAll drugs indicated by the protocol of this study, combination FOLFOX-6 (m), combination FOLFIRI (m) and cetuximab are commercially available. These drugs will be formulated, packaged, labeled and stored according to the procedures indicated by the local manufacturer, the supplier and the center.

The supply of all the medication in the trial, being commercialized drugs of habitual use in the study pathology, will be carried out through the usual channels of the National Health System, with the prior favorable opinion of the CEIC and the approval of the Center's Directorate.

Compliance with the administration of the treatment under study

When an investigational product is dispensed for administration to the subject during a study, the investigator or responsible person will determine the level of compliance with the administration of the investigational product. This subject compliance with the investigational product (e.g. amount used) will be recorded in the investigational drug administration data collection log.

### *12.2 Associated diseases*

The associated diseases, the corresponding medication and the changes that occurred in these diseases and medications, will be duly noted in the CRD.

Illnesses that occur or worsen during this period, intercurrent illnesses, will be considered as adverse events and documented on the page for this purpose in the CRD.

### *12.3. Responsibilities according to Good Clinical Practices*

12.3.1 Investigator responsabilities

The responsibilities of the principal investigator in each participating Center will be:

1. Sign the essay project.
2. Know in depth the properties of drugs.
3. Obtain the informed consent of the subjects before their inclusion in the trial.
4. Collect, record and report the data correctly.
5. Immediately report serious or unexpected adverse events to the sponsor.
6. Ensure that all persons involved will respect the confidentiality of any information about the trial subjects.
7. Report regularly to the Ethics Committee for Clinical Research on the progress of the trial.

Take responsibility for the preparation of the final test report, giving your agreement to it with your signature.

12.3.2 CRD cumplimentation rules

Data will be recorded in accordance with GCP through the electronic documentation system (electronic CRD) at the center.

The application is designed to function entirely over the Internet. All processing steps, except for the actual input and display of the data, are carried out centrally on a web / database server. In

particular, data storage will be done only centrally.

The server is located at the InterHost Data Processing Center facilities in Madrid, calle Albasanz, 71.

For data entry and results printing, the system is based on a so-called "network interface", that is, data entry forms and reports are displayed on the client computer as HTML pages (Hyper Text Markup Language, the standard language for describing pages on the Internet) through a web browser. It is not necessary to install any user-specific software in order to use the system from the investigator's computer. The raw data can be accessed directly through an ODBC database for further data processing.

The system checks the correctness of the data by ranges and performs validity and consistency checks. Implausible or omitted data can be corrected or completed after discussion with the investigator. Correction documents are stored (audit trail).

The system has a system of keys and passwords that restricts access to different areas of the application depending on the role assigned by the sponsor. Apart from the researcher, only expressly authorized persons who have received specific training for the study may complete the CRD-e.

All the data collected in the e-CRDs must be able to be documented in measurement records or through annotations in the patients' medical records.

Patient identification lists are stored exclusively at study centers. The study documents are archived at the centers. Documents must be kept for a period of 15 years.

### *12.4.Report and Publication of the Clinical Trial*

Ccomplying with the provisions of the R.D. 223/2004, the results of this test will be published, both positive and negative results in recognized scientific media.

The sponsor and the researchers are fully committed to publishing the results of the study. All publications (eg, manuscripts, abstracts, oral / slide presentations, book chapters) based on this study must be submitted to the sponsor for review prior to publication.

The trial will be registered in the public access database "clinicaltrials.gov" of the National Institute of Health of the United States of North America.

### *12.5 Monitoring and Audit*

Investigator responsibilities are stipulated in the ICH Guidelines for Good Clinical Practice (GCP).

Researchers must enter study data in the Data Collection Notebooks or other data collection system. The investigator will allow monitoring visits related to the study and audits by the Sponsor or its representatives, the review of the Ethics Committees, and the regulatory inspection (s) (e.g., FDA, EMEA) providing access direct to the facilities where the study is taking place, the original documents, the data collection notebooks, and all other documents of the study.

The investigator, or the investigator's designated member, should be available for some time during the monitoring visits to review data and resolve any queries and to allow direct access to the patient's source documents (e.g., medical history, laboratory tests, ECGs) for verification of original data. The data collection must be completed before each visit and must be made available to the sponsor's representative so that they can verify its accuracy and completeness.

### *12.6 Protocol amendment*

Supplements or changes to the protocol can be made exclusively by the sponsor, who must send them to the Ethics Committee and the AEMPS as amendments to the protocol.

### *12.7 Data management*

All data (personal, clinical, economic and from studies of biological material) obtained on patients will be treated in accordance with the Directive on the protection of people with respect to the processing of personal data and Organic Law 15/1999, of 13 December of protection of personal data.

In accordance with the provisions of the aforementioned legislation, patients may exercise their rights of access, modification, opposition and cancellation of data, for which they must contact the doctor of the clinical trial.

The content of the CRD as well as the documents generated during the study will be considered strictly confidential and will not be disclosed to third parties.

### *12.8 Documentation*

The researcher has the legal obligation to keep the patient identification list for the time stipulated in art. 39 of RD 223/2004. Likewise, the researcher must store the data of the registered patients, including the original or copies of the test results, the informed consents, the approval of the Ethics Committee, as well as the correspondence and any other original documents associated with the study, during a period specified in art. 39 of RD 223/2004. This necessary condition also applies in the event that the doctor transfers the documents (together with the associated storage obligation) to a successor.

Original study patient data (medical history) should be stored according to the applicable archiving period at the study centers, but not for a period of less than 15 years.

The researcher / s must guarantee that the relevant records and documents for the study and the distribution of the study medication, that is, copies of the data collection notebooks and original source documents, data and records (eg records hospital charts, clinical charts, laboratory notes; memos; patient diaries or evaluation checklists; pharmacy supply records; data recorded from automated instruments; certified copies or transcripts after verification as exact copies; microfiche; photographic negatives; microfilms or magnetic media, X-rays, patient files; and records kept in the pharmacy, in the laboratories, and in the technical-medical departments involved in the clinical study; documents related to the treatment of the patient and the count of the study drug; consents informed signed originals, etc.]) are on file by the investigator du For as long as necessary to comply with national and international regulations (generally 15 years after clinical development has been discontinued or after final marketing approval). The researcher agrees to comply with the document / record retention procedures by signing the protocol.

### *12.9.Finance*

GEMCAD-1002 (POSIBA) is a trial sponsored by the Spanish Multidisciplinary Group on Digestive Cancer, a non-profit scientific association. The sponsor will bear the costs of the trial (insurance, start-up, and trial monitoring).

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