Summary Table of Study Protocol

Title	ProSpective MultIcenter ObservationaL Study on the Quality of Life of mCRC *RAS* Wild-type Patients Receiving Anti-EGFR MAbs + FOLFOX or FOLFIRI as 1st Line of Treatment
Protocol version identifier	***20140383 Protocol Amendment, Version 2.0***
Date of last version of the protocol	***10 May 2017***
EU Post Authorization Study (PAS) Register No	*NA*
Active Substance	Panitumumab
Medicinal Product	Vectibix®
Product Reference	EMEA/H/C/000741
Procedure Number	EU/1/07/423
Joint PASS	*NA*
Research Question and Objectives	To assess the impact of the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients' health related quality of life (HRQoL), as measured by means of the EORTC – QLQC30 questionnaire.
Country(ies) of Study	Italy
Author	PPD Amgen S.r.l. Via Tazzoli, 6 20154 Milan ITALY

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Europe B.V.
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Investigator's Agreement

I have read the attached protocol entitled **ProSpective multIcenter observationaL study on the Quality of life of mCRC *RAS* wild-type patients receiving Anti-EGFR MAbs + FOLFOX or FOLFIRI as 1st line of treatment dated 24 Oct 2019,** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on harmonization Tripartite Guideline on Good Clinical Practice and applicable regulations/guidelines.

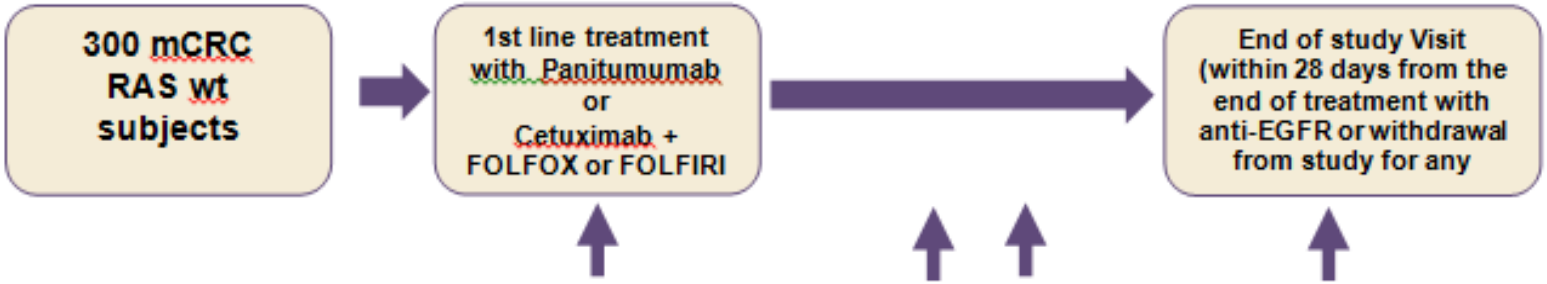
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Study Design Schema



1. Table of Contents

List of Tables

List of Appendices

2. List of Abbreviations

Abbreviation or Term	Meaning
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
BSA	Body Surface Area
DBP	Diastolic Blood Pressure
DLQI	Dermatology Life Quality Index
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
HRQoL	Health related quality of life
ICF	Informed Consent Form
ICH GCP	International Committee for Harmonization Good Clinical Practice
ICJME	International Committee of Medical Journal Editors
IRB/IEC	Institutional Review Board/ Institutional Ethics Committee
MAbs	Monoclonal Antibodies
mCRC	Metastatic colorectal cancer
QoL	Quality of Life
RAS	Rat Sarcoma Virus
PRO	Patient reported outcomes
SBP	Systolic Blood Pressure
SAE	Serious Adverse Event
WT	Wild type

3. Responsible Parties

Not Applicable

4. Abstract

- Study Title

ProSpective multIcenter observationaL study on the Quality of life of *RAS* wild- type mCRC patients receiving Anti-EGFR MAbs + FOLFOX or FOLFIRI as 1st line of treatment.

- Study Background and Rationale

Cetuximab and Panitumumab are anti-EGFR monoclonal antibodies (MAbs) indicated for the first-line treatment of *RAS* wild-type metastatic colorectal cancer (mCRC) in combination with chemotherapy doublets. Although these drugs have a more targeted and specific action on tumour cells than conventional cytotoxics, they are not devoid of side effects. In particular, cutaneous effects are frequent (50-90%) and sometimes severe. While a relevant amount of safety results have been provided by controlled clinical trials, less evidences about the incidence of adverse events and their management in the real-life scenario have been provided. Moreover, only a few data are currently available about the impact of upfront doublets plus anti-EGFR MAbs on patients' quality of life.

- Research Question and Objective(s)
  - Primary Objective(s):
    - To assess the impact of the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients' health related quality of life (HRQoL), as measured by means of the EORTC – QLQC30 questionnaire.
  - Secondary Objective(s):
    - To investigate the impact of dermatological adverse events during the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients' skin satisfaction as measured by means of the Dermatology Life Quality Index (DLQI) questionnaire.
    - To assess the tolerability of administered treatments
    - To describe the adherence to the treatment in terms of dose delays, dose reductions, number of administered cycles, average relative dose intensity of every drug.
    - To describe the management of dermatological adverse events.
    - To assess the effect on skin-related QoL of preemptive vs reactive treatment of skin toxicities.
  - Hypothesis(es)/Estimation
    - No formal hypothesis will be tested in this study.

- Study Design/Type

National, multicentric, prospective, observational trial.

- Study Population or Data Resource

RAS wild-type metastatic colorectal cancer patients candidate to first-line FOLFOX or FOLFIRI + anti-EGFR MAb as per clinical practice in around 33 Italian Centers in about **50 months of enrollment (approximately between November 2015 and December 2019**).

- Summary of *Subject* Eligibility Criteria

Inclusion criteria:

- Adult (>= 18 years old) *RAS* wild-type metastatic colorectal cancer patients candidate to receive FOLFOX or FOLFIRI plus Panitumumab or FOLFOX or FOLFIRI plus cetuximab as upfront treatment as per clinical practice.
- Willingness and ability to comply with the protocol
- Written informed consent to study procedures

Exclusion criteria:

- Patients receiving a treatment under clinical investigation may not be included in the study.
- Previous treatment with an anti-EGFR monoclonal antibody.

- Follow-up

Not applicable

- Variables and end-point
  - *OutcomeVariable(s)*

HRQoL will be measured using the EORTC QLQ-C30 questionnaire. EORTC QLQ-C30 scores reported during the treatment will be also expressed as percentage of the scores reported at baseline.

Skin satisfaction will be measured using the DLQI. The DLQI score will also be expressed as a percentage of the maximum possible score of 30. DLQI scores reported during the treatment will be also expressed as percentage of the DLQI scores reported at baseline.

Tolerability: The toxicity rate, defined as the percentage of patients, relative to the total of enrolled subjects, experiencing a specific adverse event of any grade, according to National Cancer Institute Common Toxicity Criteria (NCI CTC-AE version 4.0), will be reported. Times to onset of dermatological toxicities will be also described.

Management of dermatological toxicity: concomitant medications, both topical and systemic, adopted to prevent or treat dermatological adverse events will be recorded.

- *ExposureVariable(s)*

Treatment adherence: The percentage of delayed cycles, the percentage of cycles administered with reduced doses, the number of administered cycles, the median treatment duration and the average relative dose intensity of every planned drug will be reported.

- Study Sample Size

The sample size calculation is based on feasibility considerations.

A total sample size of 300 patients (10-12 pts/center) has been planned for this study: it is estimated that about 50% (150 pts) of them should be able to complete the QoL questionnaires during the whole treatment period. This population is estimated relevant from the scientific board and useful for a first evaluation on variability of QoL during the follow-up.

- Data Analysis

All recorded parameters will be described: absolute frequency and percentage will be calculated for qualitative variables, while mean, standard deviation, median, first and third quartile will be used to summarize quantitative variables.

To reach the primary endpoint, comparison between the QoL scores (total and partials) at different times will be done and differences in mean from basal and follow-up times will be tested with T-test (Student T-test) paired data.

Tolerability and compliance to treatments, adverse events and their management during the observational period will be described. Their effect on QoL will be evaluated with a multivariate analysis (Anova).

The level of significance will be set to $p < 0.05$.

5. Amendments and Updates

Protocol version 2 24Oct 2019

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Global			*Template used 14.0 20 May 2019*
Summary Table of study Protocol/ Page 1	*Protocol version identifier*	*Replace: 20140383 Version Amendment 1* *With: 20140383 Protocol Version 2*	*New version of the protocol*
Summary Table of study Protocol/ Page 1	*Date of last version of the protocol*	*Replace:* dated 10 May 2017 *With:* **dated 24 Oct 2019**	*Last version of the protocol amendment*
Section Investigator Agreement, page 3	*Tittle to match with the cover page and Amendment date*	*Replace:* dated 10 May 2017 *With:* **protocol ProSpective multIcenter observationaL study on the Quality of life of mCRC RAS wild-type patients receiving Anti-EGFR MAbs + FOLFOX or FOLFIRI as 1st line of treatment dated 24 Oct 2019**	*Tittle to match with the cover page and new version of the protocol amendment*
Table of contents	*9.2.4 matching* *9.2.5 baseline Period* *9.2.6 Study Follow up*		*New sections in the template*
Table of contents	*9.9.1 Information Bias*	*9.9.1 Internal Validity of Study Design: Information Bias*	*New template*
Section 4. Abstract Tittle Study Population or Data Resource	*Section 4 Study Population or Data Resource*	*Replace:* 38 months of enrollment (approximately between November 2015 and December 2018). ***With:*** **50 months of enrollment (approximately between November 2015 and December 2019**).	*New study timelines*
Section 5. Amendments and Updates	*Table with the amendment changes*	*Add: changes of amendment 2 protocol* *Add all the former protocol versions*	*Changes of the protocol amendment*
Section 6. Milestones	*New study milestones*	*Replace: end of data collection and final report of study results* *With: End of data collection: 1º Quarter 2021. Final report of study results: 4º Quarter 2021*	*New study milestones with the adjustment plan*

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Section 7 rationale and background	*These results will probably help clinicians to become more and more confident with respect to the adoption of these combinations in their routinary activity*	*These results will probably help clinicians to become more and more confident with respect to the adoption of these combinations in their routinely activity*	*Grammatical error*
Section 9.2.1 Study Period	*Months to enroll*	*Replace: 38 months* *With 50 months*	*New study milestones with the adjustment plan*
Section 9.2.1 Study Period	*End of study dates*	*Replace: will end approximately in Dec 2018. The end of study is planned for December 2019* *With:* will end approximately in **December 2019**. The end of study is planned for **December 2020**	*New timelines for the enrollment period and end of study.*
Section 9.3: End of study		*Add : or reaching cycle 56*	*New decision to end the study*
Section 9.3.1 Exposure Assessment	*The percentage of delayed cycles, the cycles administered with reduced dose, the number of administered cycles, the median treatment duration and the average relative dose intensity of every planned drug will be reported*	*The percentage of delayed cycles, the cycles administered with reduced dose, the number of administered cycles, the median treatment duration and the average relative dose intensity of anti-EGRF drug will be reported*	*No single information required, just general information*
9.4 Data sources	*Utilising*	*Utilizing*	*Grammatical error*
9.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoints	*To describe the adherence to the treatment in terms of dose delays, dose reductions, number of administered cycles, average relative dose intensity of every drug, all these parameters will be described and the single values observed will be compared with the values reported previously, to determine variations .*	*To describe the adherence to the treatment with antiEGFR in terms of dose delays, dose reductions, number of administered cycles, average relative dose intensity of every drug, all these parameters will be described and the single values observed will be compared with the values reported previously, to determine variations .*	*No single information required, just general information*

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
9.9.1Internal Validity of Study Design: Information Bias	*Information Bias*	*Internal Validity of Study Design: Information Bias*	*New tittle*
Section 10.4 Subject Decision to Withdraw	*Subject Decision to Withdraw*	*Add subjects decision to withdraw*	*New text required*
Section 11.1.2 Serious Adverse Events		*Add subject /patient*	*New text required*
Section 11.1.3 Other Safety Findings	*NA*	*Add bullets to the description*	*Bullets inserted*
Section 11.2 Safety requirements	*The investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the investigator or reported by the patient that occur after signing of the informed consent form through the final study contact are recorded in the patient's appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper) within 1 business day of investigator awareness. Safety events that are not reported as part of this study or suspected to be related to any medicinal product other than the Vectibix® should be reported to the local authority in line with the local country requirements.*	*This study is prospectively collecting information of enrolled patients. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to anti-EGFR will be collected from signing of the informed consent form to the final study contact. The investigator is responsible for recording safety events that they become aware of during study period in the patient's appropriate documentation. Collected safety events occurred after subject exposure to panitumumab, with the exception of the protocol-exempted events listed in the section below, must be submitted as individual safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper form) within 1 business day of investigator awareness.*	*New text according to new version*
Section 11.2 Safety requirements	*The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on the study Case Report Froms (CRFs) documentation where safety data may also be recorded (eg,: Event CRF).*	*The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded (eg,: Case Report Form, CRF).*	*Grammatical changes*

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Section 11.2.1 Protocol exempted Safety Information	*Non serious adverse events related to anti-EGFR (Vectibix® or Cetuximab®):skin and nails disorders and hypomagnesemia.*	*Regardless of causality, for this study all safety events experienced by the subjects exposed to panitumumab must be reported to Amgen within 1 business day of investigator awareness with the exception of the following non serious adverse events related to anti-EGFR and induced by chemotherapy as listed below:* • *Non serious adverse events related to anti-EGFR (Vectibix®):* *skin and nails disorders and hypomagnesemia.* • *Non serious adverse events induced by chemotherapy: anemia, neutropenia, neurotoxicity, diarrhea.* *The rationale for exempting the above non serious events from reporting to Amgen within 1 business day is that the safety profile of panitumumab, and chemotherapies are fully described in the respective Summary of Product Characteristics.* *If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be reported individually within 1 business day of investigator awareness.* *All safety information that is not specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame.* *Protocol-exempted events and safety events that are suspected to be related to any medicinal product other than panitumumab should be reported to the local authority in line with the local country requirements.*	*This is an observational study and the AE occurred in patients treated with Cetuximab are being collected and recorded into the database, but they must not be sent to Amgen Safety.*

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Section 13.1 Publication Policy	*NA*	*Add bullets to the description*	*Bullets inserted*
Appendix B	*NA*	*New version 4.0 of template Sample Safety Reporting Form (067756) uploaded*	*New updated version*
Appendix D	*NA*	*New version 1 of template 115199 and 115201 (pregnancy and lactation notification form)*	*New updated versions*

Amendment 1 protocol 10 May 2017

Original Protocol, 24 Jul 2015

6. Milestones

Milestone	**Planned date**
Start of data collection	*November 2015*
End of data collection	***1º Quarter 2021***
Final report of study results	***4º Quarter 2021***

7. Rationale and Background

Two anti-EGFR monoclonal antibodies are currently available for the upfront treatment of *RAS* wt mCRC patients: the chimeric IgG1 cetuximab, in combination with both FOLFOX or FOLFIRI, and the fully human IgG2 panitumumab, in combination with FOLFOX or FOLFIRI.

Although anti-EGFR monoclonal antibodies have a more targeted and specific action on tumour cells than conventional cytotoxic chemotherapy drugs, they are not devoid of side effects. In particular, cutaneous effects, tightly connected to the mechanism of action of anti-EGFR monoclonal antibodies, are frequent (50-90%) and sometimes severe. They mainly include acneiform papulopustular reactions and, more rarely, eczematiform rashes or paronychia. An active and early management of these adverse events is crucial in order to improve patients' quality of life and to guarantee an adequate adherence to the treatment. Clinical practice guidelines for the prevention and treatment of anti-EGFR-related dermatologic effects have been developed thanks to the joint effort of experts in dermatology, medical and supportive oncology.

While a robust amount of evidences has been collected with regard to the safety profile of FOLFOX/FOLFIRI plus an anti-EGFR in clinical trials conducted according to Good Clinical Practice procedures, information from the "real-life" setting about the incidence of most common adverse events and their impact on patients' quality of life is still lacking.

The use of these combinations, especially with regard to the oxaliplatin-based chemotherapy backbone, has been recently implemented in the daily Italian clinical practice. In this observational study the safety profile, in terms of incidence and grade, but also pattern of occurrence and management, of adverse events will be accurately described, as well as treatments' duration and modifications. The study will provide useful insights into the current management of patients treated with FOLFOX/FOLFIRI plus panitumumab or FOLFOX/FOLFIRI plus cetuximab in the Italian clinical practice. These results will probably help clinicians to become more and more confident with respect to the adoption of these combinations in their **routinely** activity

7.1 Diseases and Therapeutic Area

Different options are currently available as upfront choices for the systemic treatment of metastatic colorectal cancer patients. In the last years different phase III trials investigated the addition of a drug targeting the Epidermal Growth Factor Receptor (anti- EGFR) to a first-line chemotherapy doublet, leading to the approval of two anti-EGFR monoclonal antibodies: the chimeric human-murine IgG1 cetuximab and the fully human IgG2 panitumumab.

The prospective and *post-hoc* analyses of randomized trials of first-line chemotherapy with or without an anti-EGFR monoclonal antibody, show that patients bearing a mutation in *KRAS* codon 12 or 13 do not benefit from the addition of the anti-EGFR to the upfront chemotherapy doublet, so that the use of both cetuximab and panitumumab has been restricted to *KRAS* wild-type patients. More recently, a pre-specified analysis of results of the PRIME trial showed for the first time that also patients bearing a mutation in some hotspots of *KRAS* (other than codon 12 and 13) and *NRAS* genes (ie, codon 12, 13, 59, 61, 117 and 146) do not achieve benefit from the addition of cetuximab or panitumumab to first-line chemotherapy. A potential detrimental effect of adding anti-EGFRs to first-line FOLFOX was also suggested in mutated patients. On the other hand, the efficacy of anti-EGFR monoclonal antibodies was optimized in patients not bearing any mutation in *KRAS* or *NRAS* codon 12, 13, 59, 61, 117 and 146, defined as *RAS* wild-type patients. Based on these results, the European Medicines Agency further

restricted the use of both panitumumab and cetuximab to this subgroup of patients. In March 2015, the European Medicines Agency approved the extension of indication for Panitumumab FOLFIRI in 1st line. The new indication was implemented by Italian Medicines Agency on 24 February 2017.

Therefore doublet plus panitumumab or cetuximab are valuable options for the upfront treatment of *RAS* wild-type mCRC patients.

Results from a phase II (PEAK) and a phase III (FIRE-3) randomized trials comparing a chemotherapy doublet plus an anti-EGFR with a chemotherapy doublet plus the anti- Vascular Endothelial Growth Factor bevacizumab suggest that the upfront use of the anti-EGFR may be beneficial for *RAS* wild-type patients in terms of overall survival, thus further supporting the adoption of these regimens as first-line choices. These findings have not been confirmed by another phase III trial (CALGB80405) showing no significant differences between a chemotherapy doublet (mainly FOLFOX) plus cetuximab or bevacizumab in terms of OS. A higher response rate was however reported in the chemotherapy plus cetuximab group. Based on these results both chemotherapy plus an anti-EGFR or chemotherapy plus bevacizumab are valid options as upfront treatment for mCRC patients. The choice will be mainly based, on a case-by-case basis, on the treatment's objective and on patients' expectations. To this regard, the impact of the treatment on patients' quality of life, that is tightly connected to the management of occurring adverse events, as well as physicians' confidence with these regimens will be of crucial importance.

In Italy two anti-EGFR MAbs are currently approved for the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer.

Panitumumab is indicated for the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer:

- in first-line in combination with FOLFOX or FOLFIRI;
- in second-line in combination with FOLFIRI for patients who have received first- line fluoropyrimidine-based chemotherapy (excluding irinotecan);
- as monotherapy after failure of fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy regimens.

Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, *RAS* wild-type metastatic colorectal cancer:

in combination with irinotecan-based chemotherapy;

in first-line in combination with FOLFOX;

as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Dermatologic adverse events of any grade are observed in more than 90% of patients treated with panitumumab and appropriate dose reductions and delays are suggested in the case of skin symptoms ≥ G3 according to the NCI CTCAE classification.

7.2 Rationale

A few data are currently available about the impact of upfront FOLFOX/FOLFIRI plus anti-EGFR MAbs on patients' quality of life. These patients' reported outcome is extremely relevant by a clinical point of view when choosing every treatment with a palliative intent, but especially when two or more options are available and no clear advantage by one of them has been demonstrated. Since dermatological toxicities are adverse events of special interest when using anti-EGFR monoclonal antibodies, a specific tool to investigate the impact of skin alterations on patients' quality of life will be adopted. The quality of life during the treatment is certainly influenced also by the incidence and the management of adverse events. No data are currently available about the management of anti-EGFR-derived skin toxicity in Italian clinical practice.

7.3 Statistical Inference (Estimation or Hypothesis[es])

No formal hypothesis will be tested in this study. Statistical analyses will be descriptive only. No statistical inference is planned.

8. Research Question and Objectives

8.1 Primary

To assess the impact of the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients' health related quality of life (HRQoL), as measured by means of the EORTC – QLQC30 questionnaire.

8.2 Secondary

To investigate the impact of dermatological adverse events during the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients' skin satisfaction as measured by means of the Dermatology Life Quality Index (DLQI) questionnaire.

To assess the tolerability of administered treatments.

To describe the adherence to the treatment in terms of dose delays, dose reductions, number of administered cycles, average relative dose intensity of every drug.

To describe the management of dermatological adverse events.

To assess the effect on skin-related QoL of preemptive vs reactive treatment of skin toxicities.

9. Research Methods

9.1 Study Design

This is a national, multicentric, prospective, observational trial. The decision to prescribe FOLFOX or FOLFIRI plus panitumumab or FOLFOX or FOLFIRI plus cetuximab must have been freely taken by the clinician prior to the study entry for each patient included. Each physician will see his/her patients within the context of routine visits, without any special visit being organized for the purposes of the study. Therefore, the doctor-patient relationship and patient follow-up are not modified. Physicians are totally free to decide on their patients' therapeutic management.

EORTC QLQ-C30 and DLQI questionnaires will be completed by the patients at baseline (Day 1 of Cycle 1), at the first day of every other cycle (every 2 weeks) thereafter, and at "End of Study Visit" (within 28 days from the end of treatment with anti-EGFR or withdrawal from study for any reason).

Before every cycle, adverse events will be recorded and graded according to NCI CTCAE Version 4.0. Treatment's modifications in terms of cycles' delay, dose reductions or drugs' interruptions will be recorded. Concomitant approaches to prevent or treat dermatological toxicities during the treatment will be registered.

9.2 Setting and Study Population

9.2.1 Study Period

Around **50** months to enroll 300 patients

Patient's enrollment will start approximately in November 2015 and will end approximately in **December 2019**. The end of study is planned for **December 2020**.

9.2.2 Selection and Number of Sites

Around 33 Italian Oncology Centers will participate to the study.

9.2.3 Subject/Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

Adult (>= 18 years old) RAS wild-type metastatic colorectal cancer patients candidate to receive FOLFOX or FOLFIRI plus panitumumab or FOLFOX or FOLFIRI plus cetuximab as upfront treatment as per clinical practice.

Willingness and ability to comply with the protocol.

Written informed consent to study procedures.

9.2.3.2 Exclusion Criteria

Patients receiving a treatment under clinical investigation may not be included in the study.

Previous treatment with an anti-EGFR monoclonal antibody.

9.2.4 Matching

Not applicable

9.2.5 Baseline Period

Not applicable

9.2.6 Study Follow-up

Not applicable

9.3 Variables

The following information will be collected:

Screening

- Informed Consent Signature
- Inclusion and exclusion criteria verification
- Personal data: sex and date of birth.
- Medical history
- Physical examination: weight
- Previous treatment for colorectal cancer
  - Primary tumor description: date of diagnosis, TNM stage, surgery, radiotherapy, chemotherapy
  - Metastasis: date of diagnosis, metastatic sites, first-line treatment schedule, anti-EGFR

Baseline

- Physical examination: ECOG, weight and height
- Prevention of cutaneous toxicity: yes vs no
- Magnesium levels
- Concomitant medications
- AE/SAE
- Administered treatment: administered chemotherapy, administered anti- EGFR and anti-EGFR modifications
- Dermatology Life Quality Index (DLQI) questionnaire
- EORTC QLQ-C30

Study visit (repetible visit):

- Physical examination: ECOG, weight and height,
- Prevention of cutaneous toxicity: yes vs no
- Magnesium levels
- Concomitant medications
- AE/SAE
- Skin toxicity/Skin toxicity management
- Administered treatment: administered chemotherapy and chemotherapy modifications, Administered anti-EGFR and anti-EGFR modifications
- Dermatology Life Quality Index (DLQI) questionnaire
- EORTC QLQ-C30

End Of Study Visit

To be completed within 28 days (+/- 3 days) after the end of the treatment with anti-EGFR or withdrawal from study for any reason (eg, patient/investigator decision**) or reaching cycle 56:**

- Reason for end of study
- Physical examination: ECOG
- Magnesium levels
- Concomitant medications
- AE/SAE
- Skin toxicity, skin toxicity management
- Dermatology Life Quality Index (DLQI) questionnaire
- EORTC QLQ-C30

Study Interruption:

Reason for study interruption:

- Skin toxicity related to anti-EGFR
- Disease progression- Patient decision
- Investigator decision
- Death

Information available for each subject on all variables will be reported by study site staff in the study-specific sponsor database. The original data source will be patient records, from routine follow-up of subjects.

Table 1. FLOW-chart

	Screening	Baseline (Day 1 Cycle 1)	Study visit (repetible visit) Cycle 1-cicle N	End Of Study Visit
ICF signature	x			
Inclusion and exclusion criteria	x			
Personal data	x			
Medical History	x			
Physical examination	x	x	x	x
Disease Information	x			
Prevention of cutaneous toxicity		x	x	
Mg levels		x	x	x
Concomitant Medications		x	x	x
AE/SAE		x	x	x
Skin toxicity and Skin Management			x	x
Treatment administered		x	x	
(DLQI) questionnaire		x	x	x
EORTC QLQ-C30		x	x	x

9.3.1 Exposure Assessment

Treatment adherence: **The percentage of delayed cycles, the percentage of cycles administered with reduced doses, the number of administered cycles, the median treatment duration and the average relative dose intensity of anti EGFR drug will be reported.**

9.3.2 Outcome Assessment

HRQoL will be measured using the EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 includes 5 functional scales (physical, role, emotional, social, and cognitive functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms (dyspnea, sleep disturbances, constipation, and diarrhea), and perceived financial impact. For the majority of the EORTC QLQ-C30 items a 4-point Likert-type response scale is used. The only exception is the global health status/QoL scale in which a 7-point Likert-type scale is used. For ease of interpretation, all scales and individual item responses are linearly converted to a 0 to 100 scale. EORTC QLQ-C30 scores reported during the treatment will be also expressed as percentage of the scores reported at baseline.

Skin satisfaction will be measured using the Dermatology Life Quality Index (DLQI). The DLQI questionnaire includes 10 questions scored from 0 (not at all, not relevant, not answered) to 3 (very much). The DLQI score is calculated by summing the scores of each question resulting in a minimum of 0 and a maximum of 30. A higher score means an impairment of the quality of life. The DLQI score will also be expressed as a percentage of the maximum possible score of 30. DLQI scores reported during the treatment will be also expressed as percentage of the DLQI scores reported at baseline.

Tolerability: The toxicity rate, defined as the percentage of patients, relative to the total of enrolled subjects, experiencing a specific adverse event of any grade, according to National Cancer Institute Common Toxicity Criteria (NCI CTC-AE version 4.02), will be reported. Times to onset of dermatological toxicities will be also described.

Treatment adherence: The percentage of delayed cycles, the percentage of cycles administered with reduced doses, the number of administered cycles, the median treatment duration and the average relative dose intensity of every planned drug will be reported.

Management of dermatological toxicity: concomitant medications, both topical and systemic, adopted to prevent or treat dermatological adverse events will be recorded.

9.3.3 Covariate Assessment

Not applicable

9.3.4 Validity and Reliability

Not applicable

9.4 Data Sources

Data will be provided by study site staff, **utilizing** subject medical notes to abstract information in order to complete electronic CRFs in the study-specific electronic database, which will be provided by the sponsor.

9.5 Study Size

Generally the impact of treatments on cancer patients' QoL is explored in clinical studies as a marginal aspect: data are not collected systematically and no longitudinal information are available about this aspect. So, no evidence of outcomes is present in literature.

For the above reasons the study sample size is not based on mathematical or hypothesis evaluations, or power estimation, but on feasibility considerations.

- Expected number of subjects presenting selected diseases and respecting inclusion/exclusion criteria
- Enrolment capacity and management of patients from centers
- Number of patients with the same disease enrolled in other studies, and their mean follow up time observed

A total sample size of 300 patients has been planned for this study: it is estimated that about 50% (150 pts) of them should be able to complete the QoL questionnaires during the whole treatment period. This population is estimated relevant from the scientific board and useful for a first evaluation on variability of QoL during the whole treatment period.

9.6 Data Management

Data are abstracted by site staff from subject notes into an electronic database provided by the sponsor. The sponsor provides protocol-specific training to all site staff delegated to abstract subject data. An eCRF Completion Guideline is provided.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor or designee is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research.

The Clinical Monitor, or designee is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs in accordance with the local laws and regulations.

The Investigator agrees to cooperate with the Clinical Monitor, or designee to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved

9.6.1 Obtaining Data Files

Not applicable

9.6.2 Linking Data Files

Not applicable

9.6.3 Review and Verification of Data Quality

Automatic edit checks within the database and further manual review by the sponsor help to ensure quality and completeness of the data. Data queries are sent to site for clarification and resolution of discrepancies.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Primary Analysis

The primary analysis will be conducted at the end of the study.

9.7.2 Planned Method of Analysis

Outcome Variable(s):

- HRQoL will be measured using the EORTC QLQ-C30 questionnaire. EORTC QLQ-C30 scores reported during the treatment will be also expressed as percentage of the scores reported at baseline.
- Skin satisfaction will be measured using the DLQI. The DLQI score will also be expressed as a percentage of the maximum possible score of 30. DLQI scores reported during the treatment will be also expressed as percentage of the DLQI scores reported at baseline.

- Tolerability: The toxicity rate, defined as the percentage of patients, relative to the total of enrolled subjects, experiencing a specific adverse event of any grade, according to National Cancer Institute Common Toxicity Criteria (NCI CTC-AE version 4.0), will be reported. Times to onset of dermatological toxicities will be also described.
- Management of dermatological toxicity: concomitant medications, both topical and systemic, adopted to prevent or treat dermatological adverse events will be recorded.

Exposure Variable(s)

Treatment adherence: The percentage of delayed cycles, the percentage of cycles administered with reduced doses, the number of administered cycles, the median treatment duration and the average relative dose intensity of every planned drug will be reported.

9.7.2.1 General Considerations

All recorded parameters will be described: absolute frequency and percentage will be calculated for qualitative variables, while mean, standard deviation, median, first and third quartile will be used to summarize quantitative variables.

The population will be analyzed totally and stratified for treatment (FOLFOX plus panitumumab and FOLFOX plus cetuximab).

The level of significance will be set to $p < 0.05$. No interim analyses are planned for this study.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

There will be no imputation for missing data.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

Not applicable

9.7.2.3.2 Description of Subject/Patient Characteristics

Not applicable

9.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

To reach the primary endpoint (“To assess the impact of the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients’ health related quality of life”), comparison between the QoL scores (total and partials) at different times will be done and

differences in mean from basal and follow-up times will be tested with T-test (Student T-test) paired data.

EORTC-QLQ C30 score will be calculated in the total population and also in the two subgroups: FOLFOX/FOLFIRI plus panitumumab and FOLFOX/FOLFIRI plus cetuximab.

Differences in mean between the two subpopulation will be tested at different times with T-test.

- To investigate the impact of dermatological adverse events during the treatment with FOLFOX or FOLFIRI plus anti-EGFR MAbs on patients' skin satisfaction will be calculated the Dermatology Life Quality Index (DLQI) score.

Differences in mean between the two subpopulation will be tested at different times with T-test.

- To assess the tolerability of administered treatments, Tolerability and compliance to treatments will be described. Their effect on QoL will be evaluated with a multivariate analysis (Anova).
- To describe the adherence to the treatment **with antiEGFR** in terms of dose delays, dose reductions, number of administered cycles, average relative dose intensity of every drug, all these parameters will be described and the single values observed will be compared with the values reported previously, to determine variations .
- Every adverse event occurred will be described with particular attention to dermatologic ones: description, severity and management of the event will be illustrated. Correlation with number of event and treatments (FOLFOX/FOLFIRI plus panitumumab and FOLFOX/FOLFIRI plus cetuximab) will be verify with a multivariate analysis (Anova)
- Will be verified the presence of preemptive treatment of skin toxicities, and events of skin toxicities . The correlation between events of skin toxicities, QoL and presence of preemptive treatment will be tested with a multivariate analysis (Logistic)

9.7.2.5 Sensitivity Analysis

Not applicable

9.7.2.5.1 Subgroup Analysis

Not applicable

9.7.2.5.2 Stratified Analysis

Not applicable

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable

9.7.2.5.4 Other Sensitivity Analysis

Not applicable

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

Not applicable

9.8 Quality Control

Source data verification will be performed at the study site, in accordance with Amgen SOPs.

The Investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form. Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRF, informed consent forms, as applicable, and subject identification list.
- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the IRB/IEC or other relevant ethical review board and Amgen.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the contractual agreement with Amgen.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design: Information Bias

Patients will be recruited sequentially from the centers, with no selection: all patients attending to the ambulatory and fulfilling the criteria of inclusion/exclusion will be recruited. This minimizes the introduction of bias.

10. Protection of Human Subjects

10.1 Informed Consent

A copy of the proposed informed consent form is be submitted to the IRB/IEC for written approval before recruitment of subjects into the study. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits and before any protocol-specific activities are conducted. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the study.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is be documented in the subject's medical records, and the informed consent form is be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is being retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

10.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is notify the IRB/IEC of deviations from the protocol or serious adverse drug reactions occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

10.3 *Subject/Patient* Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subjects are to be identified by a unique subject identification number.

- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with Local country regulations/ICH Good Clinical Practice (GCP) Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related assessments and data.

Direct access includes examining, analyzing, verifying, and reproducing any records andreports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

10.4 Subjects Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate steps for withdrawal of their consent from the study.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the **subject/patient** at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other medically important serious event" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other medically important serious events" refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may

jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

- **Panitumumab (vial)**

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is prospectively collecting information of enrolled patients. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to anti-EGFR will be collected from signing of the informed consent form to the final study contact. The investigator is responsible for recording safety events that they become aware of during study period in the patient's appropriate documentation.

Collected safety events occurred after subject exposure to <u>panitumumab,</u> with the exception of the protocol-exempted events listed in the section below, must be

submitted as individual safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper form) within 1 business day of investigator awareness.

See Appendix B for sample Safety Report Form(s), Appendix C for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix D for sample Pregnancy and Lactation Notification Worksheets.

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded **in the** study **documentation** where safety data may also be recorded (eg,: **Case Report Form, CRF**).

11.2.1 Protocol Exempted Safety Information

Regardless of causality, for this study all safety events experienced by the subjects exposed to panitumumab must be reported to Amgen within 1 business day of investigator awareness with the exception of the following non serious adverse events related to anti-EGFR and induced by chemotherapy as listed below:

- **Non serious adverse events related to anti-EGFR (Vectibix®): skin and nails disorders and hypomagnesemia.**
- **Non serious adverse events induced by chemotherapy: anemia, neutropenia, neurotoxicity, diarrhea.**

The rationale for exempting the above non serious events from reporting to Amgen within 1 business day is that the safety profile of panitumumab, and chemotherapies are fully described in the respective Summary of Product Characteristics.

If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be reported individually within 1 business day of investigator awareness.

All safety information that is not specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame.

Protocol-exempted events and safety events that are suspected to be related to any medicinal product other than panitumumab should be reported to the local authority in line with the local country requirements.

11.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

The Sponsor will prepare the final report, including the statistical and clinical evaluations. Sponsor reserves the right to publish and present the results of this study at scientific meetings, or to submit these study data to national and international Regulatory Authorities. The investigator may not use the results of this study for publication or presentation without authorization from Sponsor.

13.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. References

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15. Appendices

Appendix A. List of Stand-alone Documents

None

Appendix B. Sample Safety Reporting Form(s)

Project ID: 20140383	AMGEN	**Observational Research Safety Reporting Form**	Date of Reporter Awareness: / Date Reported to Amgen:
		Fax reports to: Amgen Local Office 800916570	

1. Initial: ☐ Follow-up: ☐
2. Site Number: Subject Number:
3. Indicate event type: *(Please tick all that apply)* ☐ AE/Other Safety Finding ☐ Product Complaint (PC) ☐ Adverse Device Effect (ADE)

4. Contact Details (Vendor/Investigator)

Name	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

5. Reporter ID

Name or ID	Phone	Fax
Address		
City	State/Province	
Postal Code	Country	

6. HCP Contact Details (if other than reporter)

Name		
Country		
Address		
City	State/Province	Postal Code
Phone	Fax	

7. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No

Weight	Height	Race	Is patient also reporter?
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

8. Medical History (include primary diagnosis)

9. Suspect Product Information (include dosing details)

Product/Device: _____

Indication: _____

Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Prolonged Hospitalization? ☐ Yes ☐ No; Admitting dx _____; Date Admitted (day month year); Date Discharged (day month year)	Serious Criteria: #1 Fatal; #2 Immediately life-threatening; #3 Required/Prolonged hospitalization; #4 Persistent or significant disability/ incapacity; #5 Congenital anomaly/birth defect; #6 Other significant medical hazard; #7 Non serious	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (stable outcome)	Outcome: #1 Recovered/ Resolved; #2 Recovering/ Resolving; #3 Not recovered/not resolved; #4 Recovered/ resolved with sequelae; #5 Fatal; #6 Unknown	Severity: 1=mild 2=moderate 3=severe	Relationship to Product/Device: Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
								Y N	Y N
								Y N	Y N
								Y N	Y N
								Y N	Y N
								Y N	Y N
								Y N	Y N

Reporter Signature: _____ Page 1 of ____

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Reporter Signature: _____ **Page 2 of ____**

The data provided by you will be transferred as a report to Global Patient Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes

FORM-067756 Ver. #: 4.0 Effective date: 06-Nov-2017

Appendix C. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For oncology studies, the Common Terminology Criteria for Adverse Events (CTCAE) is to be used. The CTCAE is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix D. Pregnancy and Lactation Notification Worksheets

Forms must be reported to Local fax: 800916570

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐Yes ☐No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Protocol Amendment 2

Protocol Title: ProSpective MultIcenter ObservationaL Study on the Quality of Life of mCRC *RAS* Wild-type Patients Receiving Anti-EGFR MAbs + FOLFOX or FOLFIRI as 1st Line of Treatment

Amgen Protocol Number 20140383

Protocol Amendment 2, 24 October 2019

Rationale:

Changes are mainly administrative and formal clarification in the process; moreover the SAE process reporting for cetuximab was not to be part of the protocol (in an observational trial, Investigators have to notify the AE related to the marketed products, used according to the SmPC, according to the National system of PV) so we are just aligning the process to the current practice without any impact on the safety of patients and the study design and conduct.

The protocol is being amended non substantial to modify minor changes, administrative, typographical, formatting changes and formal clarification in the process of SAE reporting for cetuximab were made throughout the protocol. Updates have been implemented to align with the current template.

Description of Changes:

Table 1. Summary of Amendment Changes

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Global			*Template used 14.0 20 May 2019*
Summary Table of study Protocol/ Page 1	*Protocol version identifier*	*Replace: 20140383 Version Amendment 1* *With: 20140383 Protocol Amendment 2*	*New version of the protocol*
Summary Table of study Protocol/ Page 1	*Date of last version of the protocol*	*Replace:* dated 10 May 2017 *With:* **dated 24 Oct 2019**	*Last version of the protocol amendment*
Section Investigator Agreement, page 3	*Tittle to match with the cover page and Amendment date*	*Replace:* dated 10 May 2017 *With:* **protocol ProSpective multIcenter observationaL study on the Quality of life of mCRC RAS wild-type patients receiving Anti-EGFR MAbs + FOLFOX or FOLFIRI as 1st line of treatment dated 24 Oct 2019**	*Tittle to match with the cover page and new version of the protocol amendment*
Table of contents	*9.2.4 matching* *9.2.5 baseline Period* *9.2.6 Study Follow up*		*New sections in the template*
Table of contents	*9.9.1 Information Bias*	*9.9.1 Internal Validity of Study Design: Information Bias*	*New template*
Section 4. Abstract Tittle Study Population or Data Resource	*Section 4 Study Population or Data Resource*	*Replace:* 38 months of enrollment (approximately between November 2015 and December 2018). ***With:* 50 months of enrollment (approximately between November 2015 and December 2019**).	*New study timelines*

Table 1. Summary of Amendment Changes

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Section 5. Amendments and Updates	*Table with the amendment changes*	*Add: changes of amendment 2 protocol* *Add all the former protocol versions*	*Changes of the protocol amendment*
Section 6. Milestones	*New study milestones*	*Replace: end of data collection and final report of study results* *With: End of data collection: 1º Quarter 2021. Final report of study results: 4º Quarter 2021*	*New study milestones with the adjustment plan*
Section 7 rationale and background	*These results will probably help clinicians to become more and more confident with respect to the adoption of these combinations in their routinary activity*	*These results will probably help clinicians to become more and more confident with respect to the adoption of these combinations in their routinely activity*	*Grammatical error*
Section 9.2.1 Study Period	*Months to enroll*	*Replace: 38 months* *With 50 months*	*New study milestones with the adjustment plan*
Section 9.2.1 Study Period	*End of study dates*	*Replace: will end approximately in Dec 2018. The end of study is planned for December 2019* *With:* will end approximately in **December 2019**. The end of study is planned for **December 2020**	*New timelines for the enrollment period and end of study.*
Section 9.3: End of study		*Add : or reaching cycle 56*	*New decision to end the study*

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Table 1. Summary of Amendment Changes

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Section 9.3.1 Exposure Assessment	*The percentage of delayed cycles, the cycles administered with reduced dose, the number of administered cycles, the median treatment duration and the average relative dose intensity of every planned drug will be reported*	*The percentage of delayed cycles, the cycles administered with reduced dose, the number of administered cycles, the median treatment duration and the average relative dose intensity of anti-EGRF drug will be reported*	*No single information required, just general information*
9.4 Data sources	*Utilising*	*Utilizing*	*Grammatical error*
9.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoints	*To describe the adherence to the treatment in terms of dose delays, dose reductions, number of administered cycles, average relative dose intensity of every drug, all these parameters will be described and the single values observed will be compared with the values reported previously, to determine variations .*	*To describe the adherence to the treatment with antiEGFR in terms of dose delays, dose reductions, number of administered cycles, average relative dose intensity of every drug, all these parameters will be described and the single values observed will be compared with the values reported previously, to determine variations .*	*No single information required, just general information*
9.9.1Internal Validity of Study Design: Information Bias	*Information Bias*	*Internal Validity of Study Design: Information Bias*	*New tittle*
Section 10.4 Subject Decision to Withdraw	*Subject Decision to Withdraw*	*Add subjects decision to withdraw*	*New text required*
Section 11.1.2 Serious Adverse Events		*Add subject /patient*	*New text required*

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Table 1. Summary of Amendment Changes

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Section 11.1.3 Other Safety Findings	*NA*	*Add bullets to the description*	*Bullets inserted*
Section 11.2 Safety requirements	*The investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the investigator or reported by the patient that occur after signing of the informed consent form through the final study contact are recorded in the patient's appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper) within 1 business day of investigator awareness. Safety events that are not reported as part of this study or suspected to be related to any medicinal product other than the Vectibix® should be reported to the local authority in line with the local country requirements.*	*This study is prospectively collecting information of enrolled patients. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to anti-EGFR will be collected from signing of the informed consent form to the final study contact. The investigator is responsible for recording safety events that they become aware of during study period in the patient's appropriate documentation.* *Collected safety events occurred after subject exposure to panitumumab, with the exception of the protocol-exempted events listed in the section below, must be submitted as individual safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper form) within 1 business day of investigator awareness.*	*New text according to new version*

Table 1. Summary of Amendment Changes

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Section 11.2 Safety requirements	*The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on the study Case Report Froms (CRFs) documentation where safety data may also be recorded (e.g.: Event CRF).*	*The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded (eg,: Case Report Form, CRF).*	*Grammatical changes*
Section 11.2.1 Protocol exempted Safety Information	*Non serious adverse events related to anti-EGFR (Vectibix® or Cetuximab®):skin and nails disorders and hypomagnesemia.*	*Regardless of causality, for this study all safety events experienced by the subjects exposed to panitumumab must be reported to Amgen within 1 business day of investigator awareness with the exception of the following non serious adverse events related to anti-EGFR and induced by chemotherapy as listed below:* • *Non serious adverse events related to anti-EGFR (Vectibix®):* *skin and nails disorders and hypomagnesemia.* • *Non serious adverse events induced by chemotherapy: anemia, neutropenia, neurotoxicity, diarrhea.*	*This is an observational study and the AE occurred in patients treated with Cetuximab are being collected and recorded into the database, but they must not be sent to Amgen Safety.*

Table 1. Summary of Amendment Changes

Section	*Text in Protocol*	*Amended Text*	*<<Rationale for Change>>*
Section 11.2.1 Protocol exempted Safety Information		*The rationale for exempting the above non serious events from reporting to Amgen within 1 business day is that the safety profile of panitumumab, and chemotherapies are fully described in the respective Summary of Product Characteristics.* *If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be reported individually within 1 business day of investigator awareness.* *All safety information that is not specified in this section including all fatal events are to be collected and submitted to Amgen within the specified time frame.* *Protocol-exempted events and safety events that are suspected to be related to any medicinal product other than panitumumab should be reported to the local authority in line with the local country requirements.*	
Appendix B	*NA*	*New version 4.0 of template Sample Safety Reporting Form (067756) uploaded*	*New updated version*
Appendix D	*NA*	*New version 1 of template 115199 and 115201 (pregnancy and lactation notification form)*	*New updated versions*