



A STUDY OF FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

[MULTICENTER TRIAL]

First-line FOLFOX-4 plus panitumumab followed by 5-FU/LV plus panitumumab or single-agent panitumumab as maintenance therapy in patients with *RAS* wild-type, metastatic colorectal cancer: the VALENTINO study

Drug Name/Project No.: PANITUMUMAB

EudraCT 2015-000333-71

Protocol Number:

Sponsor: Fondazione IRCCS Istituto Nazionale dei Tumori

Study Coordinator: *Filippo de Braud*

Responsible Investigator: *M. Di Bartolomeo and F. Pietrantonio*

Statistician: *L. Mariani*

Data Management: *I. Bossi*

This study will be conducted according to the accepted standards of "Good Clinical Practice"

CONFIDENTIALITY STATEMENT:The information contained in this document is the property of Fondazione IRCCS Istituto Nazionale dei Tumori and therefore is provided to you in confidence for review by you, your staff, an applicable Ethics Committee/Institutional Review and regulatory authorities. It is understood that the information will not be disclosed to others without prior written approval from Fondazione IRCCS Istituto Nazionale dei Tumori, except to the extent necessary to obtain informed consent from those persons to whom the medication may be administered..

Reference Centre:

s.c. Oncologia Medica 1

Fondazione IRCCS Istituto Nazionale dei tumori, via G. Venezian n. 1, 20133 Milano

Fondazione IRCCS Istituto Nazionale dei Tumori – Milano

PROTOCOLLO N° INT

APPROVATO DAL COMITATO ETICO IN DATA



First-line FOLFOX-4 plus panitumumab followed by 5-FU/LV plus panitumumab or single-agent panitumumab as maintenance therapy in patients with *RAS* wild-type, metastatic colorectal cancer: the VALENTINO study

A STUDY OF FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

Fondazione IRCCS Istituto Nazionale dei Tumori - Milano

PROTOCOLLO n° INT.....

[MULTICENTER TRIAL]

Approved by the Steering Committee

Signature

Date

Dr. Filippo de Braud (INT-Milano)

Dr. Maria Di Bartolomeo (INT-Milano)

Dr. Filippo Pietrantonio (INT-Milano)

Dr. Enrico Cortesi

Dr. Francesco Di Costanzo

Dr. Sara Lonardi

Dr. Lorenza Rimassa

Dr. Salvatore Siena

Dr. Vittorina Zagonel

Dr. Alberto Zaniboni



First-line FOLFOX-4 plus panitumumab followed by 5-FU/LV plus panitumumab or single-agent panitumumab as maintenance therapy in patients with *RAS* wild-type, metastatic colorectal cancer: the VALENTINO study

A STUDY OF FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

Fondazione IRCCS Istituto Nazionale dei Tumori - Milano

PROTOCOLLO n° INT

[MULTICENTER TRIAL]

CLINICAL SITE SIGNATURE LIST

	Signature	Date
Dr..... Principal Investigator	_____	_ / _ / _
Dr..... Sub-Investigator	_____	_ / _ / _
Dr..... Sub Investigator	_____	_ / _ / _
Dr..... Sub Investigator	_____	_ / _ / _
Dr..... Sub Investigator	_____	_ / _ / _

I have thoroughly read and reviewed the study protocol VALENTINO
Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to the international good clinical practice principles and regulatory authority requirements for source document verification and auditing/inspection of the study.
I agree to use the study material, including medication, only as specified in the protocol.
I understand that any violation of the protocol may lead to early termination of the study.
I agree to the following time schedule: The study will start on May 2015 and is foreseen to be completed by May 2018.

TABLE OF CONTENTS

Protocol Synopsis
Study Design
Study Procedure
1.0 BACKGROUND AND RATIONALE
1.1 Background
1.2 Rationale for performing the study
2.0 STUDY OBJECTIVES
2.1 Primary objectives
2.2 Secondary objectives
2.3 Explorative objectives
3.0 OVERALL STUDY DESIGN
3.1 Description of the design
3.2 Number of centers
4.0 SELECTION CRITERIA
4.1 Total number of patients
4.2 Inclusion criteria
4.3 Exclusion criteria
5.0 STUDY PLAN
5.1 Study period
5.2 Assignment to treatment and registration procedures
5.3 Study duration and early termination
6.0 SAFETY AND EFFICACY CRITERIA EVALUATION
6.1 Assessment of Safety
6.2 Efficacy parameters and evaluations
6.3 Criteria of evaluation of response
7.0 STUDY MEDICATION
7.1 Drug name, Formulation, Packaging and Storage
7.2 Calculation of dose and dose administration
7.3 Dose Modifications for Toxicity
7.4 Warning and precautions
7.5 Pre-emptive treatment of skin rash
7.6 Concomitant Treatments
8.0 STUDY ASSESSMENTS

8.1 Description of Study Assessments
8.2 Tumor Tissue Samples for Exploratory Biomarkers
8.3 Blood Samples for Exploratory Biomarkers
9.0 SCHEDULE OF ASSESSMENT AND PROCEDURES
9.1 Screening and Baseline Assessments
9.2 Assessment during treatment
9.3 Assessments at End of Treatment
9.4 Follow-Up Assessments
10.0 PATIENT, STUDY, AND SITE DISCONTINUATION
10.1 Patient Discontinuation
10.2 Discontinuation from Study Drug
10.3 Withdrawal from Study
10.4 Study and Site Discontinuation
10.5 Replacement policy
11.0 SAFETY
12.0 DATA COLLECTION AND MANAGEMENT
12.1 Data quality assurance
12.2 Electronic Case Report Forms (eCRFs)
12.3 Source data documentation
12.4 Adverse Event Reporting Period
12.5 Procedure for reporting serious adverse events
12.6 Retention of records
13.0 STATISTICAL CONSIDERATIONS
13.1 Sample size calculation
13.2 Analysis of efficacy
13.3 Analysis of safety and safety population
14.0 PART II: ETHICS AND GENERAL STUDY ADMINISTRATION
15.0 REFERENCES

LIST OF APPENDICES

	Appendix I: Eastern Cooperative Oncology Group Performance Status
	Appendix II: NCI Common Toxicity Criteria (CTC) version 4.03
	Appendix III: Patients Reported Outcomes (PRA)
	Appendix IV: Flow Chart of Examinations
	Appendix V: Adverse Event Report Form Instructions
	Appendix VI: SAE Form
	Appendix VII: Declaration of Helsinki

STUDY CONTACTS

	Name Address	Tel Number Fax Number
Study Coordinator:	Dr. Filippo de Braud	Tel: 02.23902148 Fax: 02.23902149
Responsible Investigator:	Dott.ssa M. Di Bartolomeo Dott. F. Pietrantonio	Tel: 02.23902882-3807 Fax: 02.23902149
Project Statistician:	Dr. Luigi Mariani	Tel: 02.23903199

IN THE CASE OF EMERGENCY:

In case of a serious adverse event (SAE) or a similar emergency, the following responsible personnel must be contacted immediately by telephone, telex or telefax as appropriate.

Pharmacists:	Dr. E. Togliardi	Tel: 02.23902897-2335
	Dr. G. Saibene	Fax: 02.23903189

SYNOPSIS

Title of Study	First-line FOLFOX-4 plus panitumumab followed by 5-FU/LV plus panitumumab or single-agent panitumumab as maintenance therapy in patients with RAS wild-type, metastatic colorectal cancer: the VALENTINO study
Indication	Colorectal cancer
Treatment line	1 st line
Principal investigator	Dr. Filippo de Braud
Rationale	<p>First-line treatment of metastatic colorectal cancer should be administered according to the individual situation, patients' needs, therapeutic preconditions (e.g. neurotoxicity following adjuvant oxaliplatin-based chemotherapy), biomarkers and aggressiveness of the disease.</p> <p>The OPTIMOX1 trial showed an equivalent duration of disease control for a de-escalation / maintenance / reintroduction strategy compared with a treatment until progression strategy for oxaliplatin-based chemotherapy. Continuation of "lightened" fluoropyrimidine-based chemotherapy and bevacizumab represents a standard of care in the maintenance setting.</p> <p>Panitumumab with FOLFOX-4 chemotherapy represents a standard of care in the treatment of RAS wild-type metastatic colorectal cancer. The question whether the maintenance strategy might apply also to panitumumab in combination with chemotherapy is unknown at present.</p> <p>As the continuation of chemotherapy plus panitumumab until disease progression was foreseen in the hallmark "PRIME" trial, the question is whether a de-escalation of treatment intensity will not be inferior with respect to resulting time with tumor control, but allow patients a period with less toxicity and gain of quality of life.</p> <p>However, no data are available at present regarding the optimal maintenance treatment with anti-EGFR monoclonal antibodies when used in association with first-line chemotherapy.</p>
Primary endpoint	To compare the efficacy, in terms of non-inferiority of progression-free survival (PFS), of maintenance with panitumumab alone (arm B) as compared to

	panitumumab with 5-FU/LV (arm A) following induction treatment with FOLFOX-4 and panitumumab.
Secondary endpoints	<ul style="list-style-type: none"> - Safety and tolerability (according to CTCAE v 4.03). All Adverse events will be reported according to NCI Criteria. The incidence of adverse events will be summarized according to the primary system-organ class (SOC) and within the category defined in the CTCAE v4.03. The summaries will be overall (severity grades 1-4) and for grade ≥ 3 events and will also report the actions taken in terms of treatment discontinuation. Similar summaries will be made for serious adverse events. The safety set will be considered. - Quality of life (patients reported outcomes). - Response rate (RR), duration of response (DR), time to progression (TTP), time to treatment failure (TTF) and overall survival (OS). - Exploratory endpoints: Archival tumor tissue samples will be collected at baseline. Samples will be sent at Pathology Department of Fondazione IRCCS Istituto Nazionale dei Tumori for exploratory biomarkers substudy A representative formalin-fixed, paraffin-embedded (FFPE) diagnostic tumor specimen, as a tissue block that must have been reviewed by a pathologist to confirm that it contains adequate tumor tissue. In alternative, fifteen 5-micron unstained slides are allowed. Next-generation sequencing (Ion-Torrent) and in-situ hybridization techniques will be performed to identify potential biomarkers of primary resistance. Since the availability of blood-based biomarkers could be particularly useful for prediction of treatment efficacy or acquired resistance to panitumumab, in this study we will collect blood samples (optional) in individual patients (before treatment, every 8 weeks during treatment and at progression) to analyze circulating tumor DNA by digital PCR (ddPCR) or next generation (NGS) approaches. Moreover, pharmacogenetic studies to predict panitumumab and chemotherapy toxicity are planned.
Study design	Open label, randomized, multicenter, phase II study
Inclusion criteria	<p>Patients must meet the following criteria for study entry</p> <ol style="list-style-type: none"> 1. Written informed consent prior to performance of any study procedure; 2. Age ≥ 18 years; 3. ECOG Performance Status 0-1; 4. Life expectancy of at least 12 weeks in the opinion of the Investigator; 5. Histologically or cytologically confirmed adenocarcinoma of the colon or rectum, with RAS wild-type status;

	<p>6. Metastatic unresectable colorectal cancer not previously treated with standard chemotherapy for advanced or metastatic disease;</p> <p>7. Measurable or non-measurable metastatic lesion(s), as defined by RECIST version 1.1;</p> <p>8. Laboratory requirements:</p> <ul style="list-style-type: none"> - Neutrophils $\geq 1.5 \times 10^9/L$, Platelets $\geq 100 \times 10^9/L$, and Haemoglobin $\geq 10g/dL$ - Total bilirubin ≤ 1.5 time the upper-normal limits (UNL) of the Institutional normal values; ASAT (SGOT) and/or ALAT (SGPT) $\leq 2.5 \times UNL$, or $\leq 5 \times UNL$ in case of liver metastases; alkaline phosphatase $\leq 2.5 \times UNL$, $\leq 5 \times UNL$ in case of liver metastases, $\leq 10 \times UNL$ in case of bone metastases; LDH $< 1500 U/L$ - Creatinine clearance (calculated according to Cockcroft and Gault) $> 60 mL/min$ or serum creatinine $\leq 1.5 \times$ upper limit of normal (UNL); <p>9. Patients must be accessible for treatment and follow up. Patients registered on this trial must be treated and followed at the participating center.</p> <p>10. Archival tumor tissue is required for exploratory research at enrolment.</p>
<p>Exclusion criteria</p>	<p>Exclude a patient from this study if any of the following conditions are observed:</p> <ol style="list-style-type: none"> 1. Has a serious illness or medical condition(s) including, but not limited to the following: <ol style="list-style-type: none"> a. Other concurrently active malignancies excluding malignancies that are disease free for more than 5 years or carcinoma-in-situ deemed cured by adequate treatment. b. Known brain metastasis or leptomeningeal metastasis. c. Active infection (ie, body temperature $\geq 38^\circ C$ due to infection). d. Ascites, pleural effusion or pericardial fluid requiring drainage in last 4 weeks. e. Intestinal obstruction, pulmonary fibrosis or interstitial pneumonitis, renal failure, liver failure, or cerebrovascular disorder. f. Uncontrolled diabetes. g. Myocardial infarction within the last 12 months, severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV h. Gastrointestinal hemorrhage. i. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or hepatitis B or C. j. Autoimmune disorders or history of organ transplantation that require immunosuppressive therapy. k. Psychiatric disease that may increase the risk associated with study participation or study drug

	<p>administration, or may interfere with the interpretation of study results.</p> <p>2. Patients who had received adjuvant oxaliplatin-based chemotherapy and had recurrence during treatment or within 12 months from its completion are excluded. Patients who had received adjuvant fluoropyrimidine mono-therapy and had recurrence during treatment or within 6 months from its completion are excluded.</p> <p>3. Disease that is deemed potentially resectable after conversion chemotherapy is excluded. In particular, patients must be deemed unresectable by a multidisciplinary team, even when foreseeing a response to treatment. In case of liver metastases, the concept of resectability must take into account both the aim of oncological radicality (R0 resection) and remanent liver function considerations.</p> <p>4. Treatment with any of the following within the specified time frame prior to study drug administration:</p> <ul style="list-style-type: none"> a. Major surgery within prior 4 weeks (the surgical incision should be fully healed prior to study drug administration). b. Any anticancer therapy or investigational agent within prior 4 weeks c. Extended field radiation within prior 4 weeks or limited field radiation within prior 2 weeks. <p>5. Has unresolved toxicity of greater than or equal to CTCAE Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation). In particular, patients with platinum induced neurotoxicity greater than or equal CTCAE Grade 2 should be excluded.</p> <p>6. Is a pregnant or lactating female, or is planning to become pregnant during treatment and within 2 months after the end of treatment with panitumumab. Women of child-bearing potential with either positive or no pregnancy test at baseline. Women of child-bearing potential or sexually active men not willing to use contraception during study and for at least 2 months after end of treatment with panitumumab. Postmenopausal women must have been amenorrheic for at least 12 months to be considered of non-child bearing potential.</p>
<p>Treatment schema (Regimen, Dosing)</p>	<p>Induction phase with panitumumab as 1 hour intravenous infusion at the dosage of 6 mg/kg, given every two weeks, plus FOLFOX-4 chemotherapy as standard guidelines.</p> <p>Before start of FOLFOX-4 plus panitumumab, at the time of enrollment, patients will be immediately randomized electronically 1:1 to one of the two maintenance arms. Induction treatment with FOLFOX-4 plus panitumumab will continue until progressive disease, unacceptable toxicity or</p>

	<p>informed consent withdrawal, or for up to 8-12 cycles At the end of induction treatment, in presence of complete or partial response, or stable disease, non-progressing patients will be allocated to one of the two pre-assigned maintenance arms:</p> <p>A) 5-FU/LV (De Gramont regimen) plus panitumumab given at 6 mg/Kg every two weeks until progressive disease, unacceptable toxicity or informed consent withdrawal</p> <p>B) Panitumumab alone given at 6 mg/Kg every two weeks until progressive disease, unacceptable toxicity or informed consent withdrawal</p> <p>Imaging studies (thorax and abdominal CT or MRI scan) will be performed at baseline (4 weeks prior enrollment) and every 8 weeks (4 cycles) during treatment.</p>
<p>Sample size justification</p>	<p>The sample size is calculated on the basis of a non-inferiority hypothesis of median PFS with panitumumab alone as compared to 5-fluorouracil/leucovorin and panitumumab, taking into account a median PFS of 10 months observed in the PRIME trial. An overall sample size of 224 subjects (112 in the control group and 112 in the study group) achieves 90% power to detect a probability of 50% in the control group and a maximum difference of 15% in the study group, with a significance level of 0.1. The drop-out rate is 15%. The accrual pattern in the two groups is uniform (allocation 1:1).</p> <p>The study lasts for 24 months of enrollment.</p>
<p>Estimated number of sites</p>	<p>25 sites in Italy</p>
<p>Study duration</p>	<p>2 years of enrollment + 1 year of follow up</p>

STUDY DESIGN

STRATIFICATION

(prior adjuvant: No vs. Yes; number of disease sites: 1 vs ≥ 2)

RANDOMIZATION

**TUMOR ASSESSMENT AFTER 8 CYCLES
(OBJECTIVE RESPONSE OR STABLE DISEASE)**

**TUMOR ASSESSMENT EVERY 8 WEEKS UNTIL PROGRESSIVE DISEASE, UNACCEPTABLE
TOXICITY OR INFORMED CONSENT WITHDRAWAL**

STUDY PROCEDURE

Parameters	Baseline	Induction Treatment	Maintenance Treatment	End of Treatment	Follow up
		Every 2 weeks	Every 2 weeks Until PD		Every 3 months
ARM A		FOLFOX-4 panitumumab	5-FU/LV Panitumumab		
ARM B			Panitumumab		
Informed consent	X ⁴				
Medical history	X ⁴				
Physical examination and vital signs	X ³	X	X	X	X
ECOG PS	X ³	X	X	X	X
Concomitant diseases and treatments	X ⁴	X	X	X	
Toxicity evaluation		X	X	X ⁷	
ECG	X ⁴	If clinically indicated			
Hematology ¹	X ³	X	X	X	
Blood chemistry ²	X ³	X	X	X	
Pregnancy test ⁸	X ⁴	If clinically indicated			
Chest/Abdomen CT or Abdomen MRI CEA	X ⁴	X ^{5,6}	X ^{5,6}		
Tissue block collection	X				
Blood samples collection ¹⁰	X ³	X ⁶	X ⁶	X ⁶	
Patient reported outcomes (PRA) ⁹	X	X ⁶	X ⁶	X ⁶	

- White blood cell count with neutrophils, red blood cell count, hemoglobin, hematocrit and platelet count
- Bilirubin (total and direct), ASAT, ALAT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium, magnesium).
- Up to 7 days before starting of treatment
- Up to 28 days before starting of treatment
- Using the same technique performed at baseline
- Every 4 cycles (8 weeks)
- Follow up on any unresolved adverse events 28 days after last drugs intake
- All women of childbearing potential (including those who have had a tubal ligation) will have a pregnancy test at baseline and if clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- PRA will be assessed with specific questionnaires (EuroQoI EQ-5D, EORTC QLQ-C30, EORTC QLQ-CR29)
- Optional, specific informed consent to be signed by the patient

1.0 BACKGROUND AND RATIONALE

1.1 BACKGROUND

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008 [1]. The highest incidence rates are found in Australia and New Zealand, Europe, and North America, and rates are significantly higher in males than in females. Notably, CRC incidence rates are rapidly increasing in several areas historically at low risk, including Spain and a number of countries within Eastern Asia and Eastern Europe [2]. Five-year survival is highly dependent on the stage at diagnosis.

Approximately 35% of CRC patients present with Stage IV metastatic disease at the time of diagnosis, and 20%–50% with Stage II or III disease will progress to Stage IV at some point during the course of their disease [3]. Stage IV CRC carries a dismal prognosis: the 5-year survival rate is < 10% [3], and median survival time of patients given optimal supportive care without any chemotherapy is approximately 5 months.

Significant advances in the treatment of metastatic colorectal cancer (mCRC) have been achieved with combination regimens consisting of standard chemotherapeutic agents, including 5-fluorouracil (5-FU) with folinic acid (leucovorin) and either irinotecan or oxaliplatin. Infusional 5-FU with leucovorin is less toxic than bolus 5-FU administration [4] and is commonly used with oxaliplatin (FOLFOX) and irinotecan (FOLFIRI). The toxicity profiles of these regimens are different, with Grade 3/4 mucositis and nausea/vomiting, and Grade 2 alopecia occurring more frequently with FOLFIRI, and Grade 3/4 neutropenia and neurosensory toxicity occurring more frequently with FOLFOX6 [5]. Tournigand and co-workers further showed that when analyzed as first-line therapy and, following crossover on progression, as second-line therapy, the FOLFIRI and the FOLFOX6 regimens showed similar results with respect to response rates, progression-free survival (PFS), and overall survival (OS). The addition of irinotecan, oxaliplatin, and targeted agents to 5-FU has increased OS from 12 months to > 20 months [6]. The sequence of use of these agents appears less important in achieving optimal overall survival than ensuring exposure to all active drugs during the course of treatment. Multiple biologic agents against two distinct molecular targets have provided clinical benefit for patients with mCRC and are approved in the United States and the European Union: bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF); aflibercept, a VEGF-trap; and cetuximab and panitumumab, which both target the epidermal growth factor receptor (EGFR).

1.2 RATIONALE OF THE STUDY

- 5-fluorouracil (5-FU) with leucovorin (LV) and oxaliplatin (FOLFOX) is a frequently used chemotherapy regimen for the first-line treatment of metastatic colorectal cancer (CRC). Results of the phase 3 PRIME trial showed that the addition of the anti-EGFR monoclonal antibody panitumumab to FOLFOX-4 in this setting improved clinical outcome in patients whose tumours did not have mutations at *KRAS* codons 12 and 13 (i.e. exon 2) [7].
- As well as *KRAS* mutations in exon 2, tumour mutations occurring in exons 3 or 4 of *KRAS* or exons 2–4 of *NRAS* have recently also been shown to be negative predictive biomarkers in patients receiving anti-EGFR therapy with cetuximab or panitumumab in combination with doublet chemotherapy or as monotherapy in chemorefractory disease [8]. In the PRIME study, when patients with such mutations were excluded from the *KRAS* exon 2 wild-type population, a more pronounced survival benefit associated with the addition of panitumumab to FOLFOX4 was reported than before the exclusion of these patients. Since these results were invariably reproduced in several registrative trials, the use of both cetuximab and

panitumumab has been restricted by the European regulatory authority (EMA) to patients not bearing any mutation in *KRAS* or *NRAS* codon 12, 13, 59, 61, 117 and 146 hotspots, defined as *RAS* wild-type patients.

- A recently published meta-analysis including 9 RCTs across different lines of treatment confirmed the negative predictive role of *RAS* mutations and estimated a 13% reduction in the risk of death by the use of an anti-EGFR agents [9]. While the addition of an anti-EGFR MoAb to chemotherapy alone provides a clear benefit in terms of ORR, PFS and OS, when looking at the comparison of chemotherapy plus anti-EGFR *versus* chemotherapy plus bevacizumab, less consistent results were reported. Indeed, in the FIRE-3 phase III study, chemotherapy plus anti-EGFR significantly reduced the risk of death by 20% but no differences were observed in terms of PFS and ORR. The recently presented and long-awaited data from phase III CALGB/SWOG 80405 trial in the *RAS* wild-type subgroup [10], that did not confirm the significant advantage in OS in favour of the anti-EGFR, previously reported by randomized FIRE-3 [11] and PEAK [12] trials. However, based on the available evidence, anti-EGFR agents with doublet chemotherapy are considered a reasonable option in the first-line setting.
- The OPTIMOX1 trial [13] showed an equivalent duration of disease control for a de-escalation / maintenance / reintroduction strategy compared with a treatment until progression strategy for oxaliplatin-based chemotherapy. Based on the results of the CAIRO-3 [14] and AIO-KRK-0207 [15], continuation of "lightened" 5-FU chemotherapy and bevacizumab represents a standard of care in the maintenance setting following oxaliplatin-based chemotherapy plus bevacizumab.
- As the continuation of doublet chemotherapy plus anti-EGFR agents until disease progression has to be regarded as standard of care, the question is whether a de-escalation of treatment intensity or even withdrawal of treatment ("drug holiday") after a certain treatment period will not be inferior with respect to resulting time with tumor control, but allows patients a period with less toxicity and gain of quality of life. However, there is still no convincing evidence on this issue.
- Recently, the MACRO-2 phase II trial [16] showed that cetuximab alone as a maintenance therapy following induction mFOLFOX plus cetuximab was not inferior to continuation mFOLFOX plus cetuximab. However, nowadays, continuation of FOLFOX with a biologic agent until progression is not a reasonable and evidence-based strategy in the first-line setting (as also shown in the MACRO TTD phase III study) [17].

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- ❖ To compare the efficacy, in terms of non-inferiority of progression-free survival (PFS), of maintenance with panitumumab alone (arm B) as compared to panitumumab with 5-FU/LV (arm A) following induction treatment with FOLFOX-4 and panitumumab.

2.2 SECONDARY OBJECTIVES

- ❖ To evaluate toxicity and safety profile during the induction phase, and to compare them in the two arms during maintenance phase;

- ❖ To evaluate quality of life (patients reported outcomes [PRAs]) during the induction phase, and to compare it in the two arms during maintenance phase;
- ❖ To evaluate the response rate (RR), duration of response (DR), time to progression (TTP), time to treatment failure (TTF) and overall survival (OS), and to compare them in the two arms during the maintenance phase.

2.3 EXPLORATORY OBJECTIVES

- ❖ To investigate potential biomarkers and their correlation with outcome measures are as follows:

1) Change in plasma biomarkers (such as circulating DNA [ct-DNA]) and its correlation with outcomes (PFS, ORR, and OS);

2) Pharmacogenetic studies to find a potential correlation between single nucleotide polymorphisms and severity of panitumumab-related rash, chemotherapy-related toxicity, drugs dose intensity and outcomes (PFS, ORR, and OS);

3) Tissue biomarkers present at baseline and investigated with next-generation sequencing (NGS) and in-situ hybridization techniques.

3.0 OVERALL STUDY DESIGN

3.1 DESCRIPTION OF THE DESIGN

This is an open label, multicenter, phase II randomized study (see Statistical Considerations). Patients will be assigned to a treatment arm by randomization and the treatment allocation will be assigned by central randomization. Before randomization the patients will be stratified by number of disease sites (1 vs. ≥ 2) and previous adjuvant therapy (no vs. yes).

The study regimens include:

INDUCTION PHASE:

- **Panitumumab** will be given by intravenous infusion at the dose of **6 mg/kg** on day 1 every 2 weeks (q2w).
- **Oxaliplatin** will be given by intravenous infusion at the dose of **85 mg/mq** on day 1 every 2 weeks (q2w).
- **Leucovorin (LV)** will be administered by intravenous infusion at the dose of **200 mg/mq** on days 1 and 2 every 2 weeks (q2w).
- **5-fluorouracil (5-FU)** will be administered by intravenous bolus injection at the dose of **400 mg/mq/day** followed by continuous infusion at the dose of **600 mg/mq/day** on days 1 and 2 every 2 weeks (q2w).

MAINTENANCE PHASE ARM A:

- **Panitumumab** will be given by intravenous infusion at the dose of **6 mg/kg** on day 1 every 2 weeks (q2w).
- **Leucovorin (LV)** will be administered by intravenous infusion at the dose of **200 mg/mq** on days 1 and 2 every 2 weeks (q2w).
- **5-fluorouracil (5-FU)** will be administered by intravenous bolus injection at the dose of **400 mg/mq/day** followed by continuous infusion at the dose of **600 mg/mq/day** on days 1 and 2 every 2 weeks (q2w).

MAITENANCE PHASE ARM B:

- **Panitumumab** will be given by intravenous infusion at the dose of **6 mg/kg** on day 1 every 2 weeks (q2w).

Patients are randomized in arm A or arm B at the time of enrollment (i.e. before the start of induction phase) and are planned to receive up to a maximum of 8 cycles. In case of objective response (partial response [PR] *plus* complete response [CR]) or stable disease (SD), patients will be treated in the maintenance phase with 5-FU/LV and panitumumab (ARM A) or panitumumab alone (ARM B) until progressive disease, consent withdrawal or unacceptable toxicity.

If a patient's tumor becomes operable, and resection is planned, the patients should be withdrawn from the study treatment.

3.2 NUMBER OF STUDY CENTERS

This is a multicenter clinical trial with planned number of centers being approximately 25.

4.0 SELECTION CRITERIA

4.1 TOTAL NUMBER OF PATIENTS

Up to 224 patients will be enrolled.

4.2 INCLUSION CRITERIA

Patients must meet the following criteria for study entry

1. Written informed consent prior to performance of any study procedure;
2. Age ≥ 18 years;
3. ECOG Performance Status 0-1 (Appendix I);
4. Life expectancy of at least 12 weeks in the opinion of the Investigator;
5. Histologically or cytologically confirmed adenocarcinoma of the colon or rectum, with *RAS* wild-type status;
6. Metastatic unresectable colorectal cancer not previously treated with standard chemotherapy for advanced or metastatic disease;
7. Measurable or non-measurable metastatic lesion(s), as defined by RECIST version 1.1;
8. Laboratory requirements:
 - Neutrophils $\geq 1.5 \times 10^9/L$, Platelets $\geq 100 \times 10^9/L$, and Haemoglobin $\geq 10g/dL$
 - Total bilirubin ≤ 1.5 time the upper-normal limits (UNL) of the Institutional normal values; ASAT (SGOT) and/or ALAT (SGPT) $\leq 2.5 \times UNL$, or $\leq 5 \times UNL$ in case of liver metastases; alkaline phosphatase $\leq 2.5 \times UNL$, $\leq 5 \times UNL$ in case of liver metastases, $\leq 10 \times UNL$ in case of bone metastases; LDH $< 1500 U/L$
 - Creatinine clearance (calculated according to Cockcroft and Gault) $> 60 mL/min$ or serum creatinine $\leq 1.5 \times$ upper limit of normal (UNL);
9. Patients must be accessible for treatment and follow up. Patients registered on this trial must be treated and followed at the participating center.
10. Archival tumor tissue is required for exploratory research at enrollment.

4.3 EXCLUSION CRITERIA

Exclude a patient from this study if any of the following conditions are observed:

1. Has a serious illness or medical condition(s) including, the following:

- a. Other concurrently active malignancies excluding malignancies that are disease free for more than 5 years or carcinoma-in-situ deemed cured by adequate treatment.
 - b. Known brain metastasis or leptomeningeal metastasis.
 - c. Active infection (ie, body temperature $\geq 38^{\circ}\text{C}$ due to infection).
 - d. Ascites, pleural effusion or pericardial fluid requiring drainage in last 4 weeks.
 - e. Intestinal obstruction, pulmonary fibrosis or interstitial pneumonitis, renal failure, liver failure, or cerebrovascular disorder.
 - f. Uncontrolled diabetes.
 - g. Myocardial infarction within the last 12 months, severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV
 - h. Gastrointestinal hemorrhage.
 - i. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or hepatitis B or C.
 - j. Autoimmune disorders or history of organ transplantation that require immunosuppressive therapy.
 - k. Psychiatric disease that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results.
2. Patients who had received adjuvant oxaliplatin-based chemotherapy and had recurrence during treatment or within 12 months from its completion. Patients who had received adjuvant fluoropyrimidine mono-therapy and had recurrence during treatment or within 6 months from its completion.
 3. Disease that is deemed potentially resectable after conversion chemotherapy.. In particular, patients must be deemed unresectable by a multidisciplinary team, even when foreseeing a response to treatment. In case of liver metastases, the concept of resectability must take into account both the aim of oncological radicality (R0 resection) and remanent liver function considerations.
 4. Treatment with any of the following within the specified time frame prior to study drug administration:
 - a. Major surgery within prior 4 weeks (the surgical incision should be fully healed prior to study drug administration).
 - b. Any anticancer therapy or investigational agent within prior 4 weeks
 - c. Extended field radiation within prior 4 weeks or limited field radiation within prior 2 weeks.
 5. Unresolved toxicity of greater than or equal to CTCAE Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation). In particular, patients with platinum induced neurotoxicity greater than or equal CTCAE Grade 2 should be excluded.
 6. Is a pregnant or lactating female, or is planning to become pregnant during treatment and within 2 months after the end of treatment with panitumumab. Women of child-bearing potential with either positive or no pregnancy test at baseline. Women of child-bearing potential or sexually active men not willing to use contraception during study and for at least 2 months after end of treatment with panitumumab. Postmenopausal women must have been amenorrheic for at least 12 months to be considered of non-child bearing potential.

5.0 STUDY PLAN

5.1 STUDY PERIOD

This study is expected to start in May 2015 and should be completed by May 2018 (24 months of enrollment and 12 months of follow-up). It is understood that these accrual rates are based on reasonable planning expectations.

5.2 ASSIGNMENT TO TREATMENT AND REGISTRATION PROCEDURES

Once informed consent is signed by the patient, screening is completed and eligibility is verified, an email is sent to the Sponsor contacts (Dr. Ilaria Bossi - ilaria.bossi@istitutotumori.mi.it; or Dr. Filippo Pietrantonio - filippo.pietrantonio@istitutotumori.mi.it) and patients are randomized electronically by means of the eCRF. The Sponsor confirms the eligibility and the treatment arm is assigned via eCRF.

5.3 STUDY DURATION AND EARLY TERMINATION

If the study will be prematurely discontinued the enrolled patients can continue study treatments (at physician discretion). A follow up on the so far treated patients will be performed and a final study report will be written with the available data.

6.0 EVALUATION OF SAFETY AND EFFICACY CRITERIA

6.1 ASSESSMENT OF SAFETY

All enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist in medical interviews, recording of adverse events, physical examinations, and laboratory measurements (hematology, biochemistry).

Patients will be evaluated for adverse events, serious adverse events, and any adverse event requiring treatment interruption or discontinuation. Patients who, at time of progression, have an ongoing adverse event leading to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different anti-tumor therapy.

All adverse events encountered during the clinical study will be reported on the electronic Case Report Form (eCRF). An adverse event is any adverse change from the patient's baseline (pre-treatment) condition, including intercurrent illness, which occurs during the course of a clinical study after treatment has started, whether considered related to treatment or not.

The intensity of clinical adverse events will be graded according to the **NCI Common Toxicity Criteria (CTC) version 4.03** grading system in the toxicity categories that have recommended gradings (Appendix II). In addition to intensity, the duration, the relationship to the trial medication, the action taken regarding the drug administration, any treatment given for the adverse event, as well as the outcome of the adverse event must be reported in the eCRF.

6.2 EFFICACY PARAMETERS AND EVALUATIONS

RECIST criteria version 1.1 will be used for response assessment [18]. Response to induction treatment has to be assessed **every 8 weeks** by using the same techniques performed at baseline. During the maintenance phase, tumor assessments will be performed every 8 weeks until PD, patients informed consent withdrawal or refusal or unacceptable toxicity. For all patients who go off study for refusal or unacceptable toxicity, tumor assessment will be continued every 8 weeks until PD. After PD, follow up visits will continue until patient's death to collect survival data every 12 weeks.

Disease Measurability

At baseline, each evaluable tumor lesion will be categorized in measurable or nonmeasurable.

Evaluable measurable lesions

- **Tumor lesions:** tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray.

- **Malignant lymph nodes:** to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Evaluable nonmeasurable lesions

The non-measurable lesions include small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions (leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly that are not confirmed and followed by imaging techniques).

Bone lesions, cystic lesions and lesions previously treated with local therapy require particular comment.

Bone Lesions: Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic Lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Not evaluable lesions

Lesions with prior local treatment: Tumor lesions that are situated in a **previously irradiated area, or in an area subjected to other loco-regional therapy**, might not be considered measurable.

6.3 CRITERIA FOR EVALUATION OF RESPONSE

Definitions of Evaluability

To be evaluable for response, patients must have received a minimum of **8 weeks** of treatment (**4 cycles**) with at least one follow-up tumor assessment unless "early

progression" occurs in which case they will be considered evaluable. Patients on therapy for at least this period will have their response classified according to the definitions set out below.

Response Criteria

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. All other lesions (or sites of disease), including pathological lymph nodes, should be identified as *non-target lesions* and should also be recorded at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected. In case of lymph nodes, only the short axis of diameter ≥ 15 meets the criterion of target lesion. In fact, a sum of the diameters (longest for non-nodal lesions and short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*.

Evaluation of target lesions

Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or not-target) must have reduction in short axis to **<10 mm**.

Partial Response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as a reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started.

Evaluation of non target lesions

Complete response (CR): the disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: the persistence of one or more non-target lesions and/or the maintenance of tumor marker level above the normal limits.

Progressive disease (PD): the appearance of one or more new lesions and/or unequivocal progression of existing non target lesions

Target lesions	Non-target lesions	New lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non PD or not all evaluated	No	PR
SD	Non PD or not all evaluated	No	SD
Non all evaluated	Non-PD	NO	inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Determination of Overall Response

Best overall response is the best response designation recorded from the start of treatment until disease progression.

Complete and partial responses have to be confirmed by two evaluations of the disease, taken at SD is only accepted if they are determined by two observations not less than 4 weeks apart.

Duration of Response (DR)

The duration of overall response is measured from the time that measurement criteria are met for complete response or partial response until the first date that recurrent or progressive disease is objectively documented. Stable disease is measured from the start of the treatment until the criteria for disease progression are met.

Time to Progression (TTP)

From the first day of treatment to progression, or death due to any cause, or last contact patient was known to be progression free or alive. Patients with no tumor assessments after baseline but who are still alive at the time of the clinical cutoff will be censored at day 1. For patients who undergo surgery after experiencing a sufficient shrinkage of the tumor, any relapse, new occurrence of colorectal cancer, or death will be considered as an event. Patients undergoing surgery without any such event will be censored at the date of the last tumor assessment that documented that neither a relapse nor a new colorectal cancer has occurred.

Time to Treatment Failure (TTF)

The analysis follows the algorithm of the aforementioned general approach for the analysis of TTP with the difference that patients who withdrew prematurely due to adverse events, insufficient therapeutic response, death, failure to return, refusing treatment/being unwilling to cooperate/withdrawing consent, will be regarded as events as well. The time to event is the time from first day of treatment to the first occurrence of any of the above events. In case of censoring, the earlier of the date of the last tumor assessment and the date of the last intake of study medication will be used.

Overall Survival

Time between the date of first day of treatment and the date of death from any cause or the last date the patient was known to be alive.

7.0 STUDY MEDICATIONS

7.1 Drug name, Formulation, Packaging and Storage

In the induction phase, oxaliplatin, leucovorin, 5-fluorouracil and panitumumab will be used via commercial supply with no study specific label.

In the maintenance phase, panitumumab will be supplied by Amgen. In arm A, leucovorin and 5-fluorouracil will be used via commercial supply with no study specific label.

Description of Investigational Product

Panitumumab is a human immunoglobulin G2 (IgG2) monoclonal antibody directed against human Epidermal Growth Factor Receptor (EGFR).

Packing and Formulation

Panitumumab will be manufactured and packaged by Amgen and distributed using Amgen's clinical investigational product distribution procedures. The 0.2 or 0.22-micron in-line filters for filtration of panitumumab will be obtained by the study centre.

Panitumumab is supplied in single-use vials (type I glass) with an elastomeric stopper, aluminium seal flip-off plastic cap. It will be presented as a sterile, aqueous, colourless, preservative-free, pH 5.6 to 6 liquid. The formulation is 20 mg/mL panitumumab, 50 mM sodium acetate trihydrate, 100 mM sodium chloride, and water for injection. Each box of panitumumab will contain either 100 mg of panitumumab in 5 mL (24 vials per box), 200 mg in 10 mL (12 vials per box) or 400 mg in 20 mL (6 vials per box).

Receipt and Storage of Investigational Product

To ensure stability of the IP it must be stored under the conditions specified below.

Panitumumab must be stored in the original carton under refrigeration at a temperature between 2°C and 8°C until the time of use. The set point for the refrigerator should be at 5°C.

Refrigerator Set Point (°C)	Acceptable Parameters:	Acceptable Range:
5°C	(± 3°C)	2°C to 8°C

Do not freeze the IP and do not shake the product excessively. Protect the vials from sunlight and do not administer the IP if discolouration is observed.

Records of the actual storage conditions during the study must be maintained. The following information should be captured:

- Records of the date and time and initials of person checking,
- 'working day' temperature of the refrigerator used for storage of the IP,
- continuous temperature recordings or regularly maintained alarm system used in conjunction with temperature monitoring.

7.2 Calculation of dose and dose administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

All drugs are to be administered via secure intravenous access (for example central vein catheter).

INDUCTION PHASE (FOLFOX-4 and panitumumab)

Panitumumab will be administered as a **6 mg/kg** intravenous infusion over 60 minutes (**day 1**) every 2 weeks. The dose of panitumumab should be administered prior to chemotherapy.

Oxaliplatin will be administered as a **85 mg/m²** intravenous infusion over 120 to 180 minutes (**day 1**) every 2 weeks. **Leucovorin** will be administered as a **200 mg/m²** intravenous infusion over 120 minutes (**day 1 and 2**) every 2 weeks. **5-fluorouracil** will be administered as a **400 mg/m²** intravenous bolus injection (**day 1 and 2**) followed by **600 mg/m²** 22-hours continuous infusion (**day 1 and 2**), every 2 weeks. Cycle length is 2 weeks +/- 3 days.

MAINTENANCE PHASE (ARM A: 5-FU/LV and panitumumab)

Panitumumab will be administered as a **6 mg/kg** intravenous infusion over 60 minutes (**day 1**) every 2 weeks. The dose of panitumumab should be administered prior to chemotherapy. **Leucovorin** will be administered as a **200 mg/m²** intravenous infusion over 120 minutes (**day 1 and 2**) every 2 weeks. **5-fluorouracil** will be administered as a **400 mg/m²** intravenous bolus injection (**day 1 and 2**) followed by **600 mg/m²** 22-hours continuous infusion (**day 1 and 2**), every 2 weeks. Cycle length is 2 weeks +/- 3 days.

MAINTENANCE PHASE (ARM B: panitumumab)

Panitumumab will be administered as a **6 mg/kg** intravenous infusion over 60 minutes (**day 1**) every 2 weeks. Cycle length is 2 weeks +/- 3 days.

Dose Calculation and Preparation Process

In order to ensure the safety of the clinical study subject it is extremely important that the IP is stored, dispensed, prepared, administered, and/or destroyed in accordance with the instructions provided.

Dose Calculation

All doses will be prepared by qualified and, where applicable, licensed health care professionals.

Drug Preparation Instructions

Panitumumab must be prepared and administered by a qualified and where applicable licensed healthcare professional. Strict adherence to aseptic technique should be used during the preparation and administration of panitumumab.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not shake the vial. Do not administer if discoloration is observed. Although panitumumab should be colourless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration).

The starting panitumumab dose is 6 mg/kg. The total dose may be rounded up or down by no greater than 10 mg. The dose of panitumumab will be calculated based on the subject's actual body weight at baseline and re-calculated at subsequent doses per institutional guidelines. At a minimum, the dose will be re-calculated if the actual body weight changed by at least $\pm 10\%$ from the last time the dose was calculated.

Before infusion, the IP must be diluted in pyrogen-free 0.9% sodium chloride for injection using aseptic technique to a recommended total volume of 100 mL. Doses higher than 1000 mg should be diluted to 150 mL (unless otherwise described in the protocol). The maximum concentration of the final solution to be infused should not exceed 10 mg/mL. The volume of normal saline should be increased as needed to ensure that the maximum concentration of the diluted solution does not exceed 10 mg/mL. The diluted solution should be mixed by gentle inversion. Do not shake or vigorously agitate the IV bag.

The IV bag should be labelled per site pharmacy Standard Operating Procedures and promptly forwarded for infusion.

Since the IP does not contain any preservative, any unused portion remaining in the vial must be discarded. The diluted product should be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored refrigerated at 2°C - 8°C. Do not freeze the diluted solution.

Administration Instructions

Subjects should be clinically assessed for toxicity prior to each dose using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.04, with the exception of skin- or nail-related toxicities, which must be graded using CTCAE version 3.04 with modifications. Complete blood count with differential and chemistry panels must be obtained ≤ 3 days before the dose of panitumumab on day 1 of each cycle, and the results must be checked before each treatment. Dosing must only occur if these test values are acceptable.

Panitumumab must be administered IV by an infusion pump or a gravity drip through a peripheral line or indwelling catheter using a non-pyrogenic, low protein binding filter with a 0.2 or 0.22 micron in-line filter infusion set-up over 60 (± 15) minutes by a trained healthcare professional.

If the first infusion is well tolerated (ie without any serious infusion-related reactions) all subsequent infusions may be administered over 30 \pm 10 minutes. It is recommended that doses higher than 1000 mg should be infused over 60 to 90 \pm 15 minutes.

Dispensing and Administration of Prepared IP

- In order to ensure the safety of the clinical study subject it is extremely important that the IP is stored, dispensed, administered and/or destroyed in accordance with the instructions provided.
- IP must be properly labeled in accordance with current ICH GCP and local/regional requirements prior to dispensing for administration.
- Only individuals listed on the Delegation of Authority Form (DoA) as authorized to prescribe, prepare and administer IP may do these activities.
- Adequate source documentation (in addition to IP accountability logs) per GCP and ICH guidelines regarding IP administration must be maintained by the clinical site staff for review and inspection by the Clinical Monitor at each visit. This may include medical records, prescriptions, medication orders, medication flow sheets, dose calculation and preparation worksheet(s) etc.

Product Complaints

Amgen would like you to report any concerns or irregularities about the packaging, appearance or usage of IP by contacting the NASCR representative. Amgen is interested in hearing about any concern or irregularity at any state of the study. Should any such concerns or irregularities occur please do not use the IP until Amgen confirms that it is permissible to use.

The following could be considered potential product complaints that need to be reported to Amgen:

- Packaging: for example, broken container or cracked container
- Devices: issues with delivery of IP by device
- Usage: for example, subject or healthcare provider can not appropriately use the product
- Labeling: for example, missing labels, illegible labels, incorrect labels, and/or suspect labels
- Change in IP appearance: for example color change or presence of foreign material

- Unexpected quantity in bottle: for example number of tablets or amount of fluid
- Evidence of tampering or stolen material

If possible, please have the IP available for examination when making the call for a product complaint. Maintain IP at appropriate storage conditions described in this manual until further instructions are received from Amgen. You will also be asked for the following, site location and name of institution/investigator, protocol number, product name, lot number (from label), date problem was noticed, a full description of the problem and whether or not a subject was dosed with the impacted product.

Panitumumab will be administered at a fixed dose of **6 mg/kg every 2 weeks**. The dose for panitumumab will be calculated as milligrams per kilogram body weight (mg/kg). The subject's weight at screening will be used to determine the dose of panitumumab to be used for the duration of the study. If the subject's weight changes by $\geq 10\%$ during the course of the study, the dose of panitumumab will be recalculated.

The **FOLFOX-4** chemotherapy doses will be calculated according to baseline body surface area (BSA) for all cycles. If there is a 10% decrease in body weight comparing to baseline, the BSA will be recalculated. If the calculated BSA is $>2.2 \text{ m}^2$, the doses to be given to the patients will be calculated according to $\text{BSA} = 2.2 \text{ m}^2$. No ideal body weight should be used for the calculation of BSA.

7.3 Dose Modifications for Toxicity

General Notes Regarding Dose Modifications

Toxicity will be graded according to the **NCI CTC AE Version 4.03**.

Guidelines to be followed in the case of a delay in treatment or dose modification (i.e. after an adverse event) are described in the following subsections. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

- For any adverse event already **present at baseline**, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered a shift of one grade and treated as a grade 1 toxicity for dose modification purposes.
- For toxicities which are considered by the investigator unlikely to develop into serious or life-threatening events (e.g. alopecia, altered taste etc.), treatment will be continued at the same dose without reduction or interruption. In addition, **no dose reductions or interruptions will be required for anemia** (non-hemolytic) as it can be satisfactorily managed by transfusions or erythropoietin. Where several toxicities with different grades or severity occur at the same time, the dose modifications applied should be the greatest reduction applicable.
- If, in the opinion of the Investigator, a toxicity is considered to be due solely to one drug (e.g. hand-foot syndrome secondary to 5-fluorouracil, skin rash due to panitumumab), the **dose of the other drugs does not require modification**.
- If a delay related to a treatment alone is required, **the other study drug(s) should be delayed as well**. Panitumumab should be restarted only when the requirements for restarting the therapy are met.

- Dose modifications for isolated **abnormal hematologic lab values** will be based on hematological parameters at start of a treatment cycle. If toxicity requires a dosing delay or interruption of all study drugs for more than four weeks, the patient will be withdrawn from the study for toxicity reasons.
- If oxaliplatin must be discontinued permanently due to neurotoxicity before the 8th cycle of FOLFOX-4 and panitumumab, the patient will be out of study due to unacceptable toxicity. If FOLFOX-4 and panitumumab (or even a single study drug component, i.e. oxaliplatin, 5-FU and/or panitumumab) must be discontinued permanently during the induction phase due to unacceptable toxicity, the patient will be out of study due to unacceptable toxicity. The patient can continue any treatment as per local standard practise and must be followed up with the study procedures.

Chemotherapy Dose Modifications – FOLFOX-4

FOLFOX4 Dose Levels

Doses of 5-FU and oxaliplatin may be adjusted depending on an individual subject's tolerance. The dose of leucovorin will remain fixed at 200 mg/m² racemate (or 100 mg/m² *l*-LV). Tables 1 to 3 indicate recommended dose levels and modification guidelines for oxaliplatin and 5-FU for non-neurological and neurological toxicity.

Table 1. FOLFOX4 Dose Reductions – Non-Neurological Toxicity

	Starting Dose	Dose Level –1	Dose Level –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	600 mg/m ²	500 mg/m ²	400 mg/m ²

Table 2. FOLFOX4 Dose Modification Guidelines

Toxicity NCI Grade* (Value)	Dose Level for Subsequent Cycles Based on Interval Toxicity**	At Time of Retreatment
No toxicity	Maintain dose level	Maintain dose level
Neutropenia (ANC) Grade 1 (ANC <LLN - $1.5 \times 10^9/L$) Grade 2 (ANC $1.5 \times 10^9/L$ - $1.0 \times 10^9/L$) Grade 3 (ANC $1.0 \times 10^9/L$ – $0.5 \times 10^9/L$) Grade 4 (ANC < $0.5 \times 10^9/L$)	Maintain dose level Maintain dose level Decrease both 5-FU & OXAL 1 dose level Decrease both 5-FU & OXAL 1 dose level	If ANC < $1.5 \times 10^9/L$ at start of cycle, hold and check weekly then treat based on interval toxicity. If ANC < $1.5 \times 10^9/L$ after 4 weeks, discontinue therapy.
Thrombocytopenia Grade 1 (PLT < LLN - $75.0 \times 10^9/L$) Grade 2 (PLT $75.0 \times 10^9/L$ - $50.0 \times 10^9/L$) Grade 3 (PLT $50.0 \times 10^9/L$ - $25.0 \times 10^9/L$) Grade 4 (PLT < $25.0 \times 10^9/L$)	Maintain dose level Maintain dose level Decrease both 5-FU & OXAL 1 dose level Decrease both 5-FU & OXAL 1 dose level	If PLT < $75.0 \times 10^9/L$ at start of cycle, hold and check weekly then treat based on interval toxicity. If PLT < $75.0 \times 10^9/L$ after 4 weeks, discontinue therapy.
Neutropenic fever ANC < $1.0 \times 10^9/L$ (i.e. Grade 3 or 4 neutropenia) & fever $\geq 38.5^\circ C$	Decrease both 5-FU & OXAL 1 dose level	
Other hematologic toxicities	Dose modifications for leukopenia at the start of subsequent courses of therapy and at time of retreatment are also based on NCI toxicity criteria (CTC Version 3.0) and are the same as recommended for neutropenia above.	
Diarrhea Grade 1 Grade 2 Grade 3 Grade 4	Maintain dose level Maintain dose level Decrease both 5-FU & OXAL 1 dose level Decrease both 5-FU & OXAL 1 dose level	If Grade 2 diarrhea at start of cycle, hold and check weekly then treat based on interval toxicity. If Grade 2 diarrhea after 4 weeks, discontinue therapy.
Other nonhematologic toxicities ^{1,2}	Dose modifications for other nonhematologic toxicities at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI toxicity criteria (CTC version 3.0) and are the same as recommended for diarrhea above.	

* National Cancer Institute Common Toxicity Criteria (CTC Version 3.0). □

** Refers to initial dose used in previous course. □1 For mucositis/stomatitis decrease only 5-FU, not Oxaliplatin. Exceptions: alopecia, fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, viral infections.

Table 3. Dose Modification Guidelines Oxaliplatin-Associated Neurotoxicity

Toxicity (Grade)	Duration of Toxicity		Persistent (Not Resolved Between Cycles)
	1 - 7 Days	> 7 Days	
Paresthesias/dysesthesias ¹ 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	Decrease to 65 mg/m ²
Paresthesias/dysesthesias ¹ with pain or with functional impairment that also interfere with ADL (Grade 3)	1st time: Decrease to 65 mg/m ² 2nd time: Decrease to 40 mg/m ²	STOP	STOP
Persistent paresthesias /dysesthesias that are disabling or life-threatening (Grade 4)	STOP	STOP	STOP
Pharyngo-laryngeal dysesthesias	No Change	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours

Panitumumab Dose Modifications

In case of toxicity Panitumumab administration may need to be withheld, reduced, or delayed (administered at > 14 day intervals). On resolution, a limited number of attempts to re-escalate reduced panitumumab doses will be allowed (outlined in Figure 1). Panitumumab dose reductions are listed in Table 4.

Table 4. Panitumumab Dose Reductions

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/kg	6	4.8	3.6

Criteria for Withholding a Dose of Panitumumab

Skin- or nail-related toxicities:

- Symptomatic skin- or nail-related toxicity requiring narcotics, systemic steroids, or felt to be intolerable by the subject
- Skin or nail infection requiring IV antibiotic or IV antifungal treatment
- Need for surgical debridement
- Any skin- or nail-related serious adverse event

Non-skin- or nail-related toxicities:

- Any grade 3 or 4 toxicity with the following exceptions:

- o Panitumumab will be withheld for symptomatic hypomagnesemia and/or hypocalcemia that persists despite magnesium and/or calcium replacement
- o Panitumumab will be withheld for grade 3 or 4 nausea, diarrhea, or vomiting that persists despite adequate supportive care
- o Panitumumab will be withheld for grade \geq 3 anemia or grade 4 thrombocytopenia that can not be managed by transfusion(s) or cytokine therapy

Criteria for Re-treatment with Panitumumab

Skin- or nail-related toxicities:

Panitumumab administration may be restarted once:

- The adverse event has improved to \leq Grade 2 (Appendix F) or returned to baseline, or;
- The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; or,
- Systemic steroids are no longer required, or
- IV antibiotic or IV antifungal treatment is no longer required

Non-skin- or nail-related toxicities:

Panitumumab administration may be restarted once the adverse event has improved to \leq Grade 1 or returned to baseline

Dose Modification Schedule

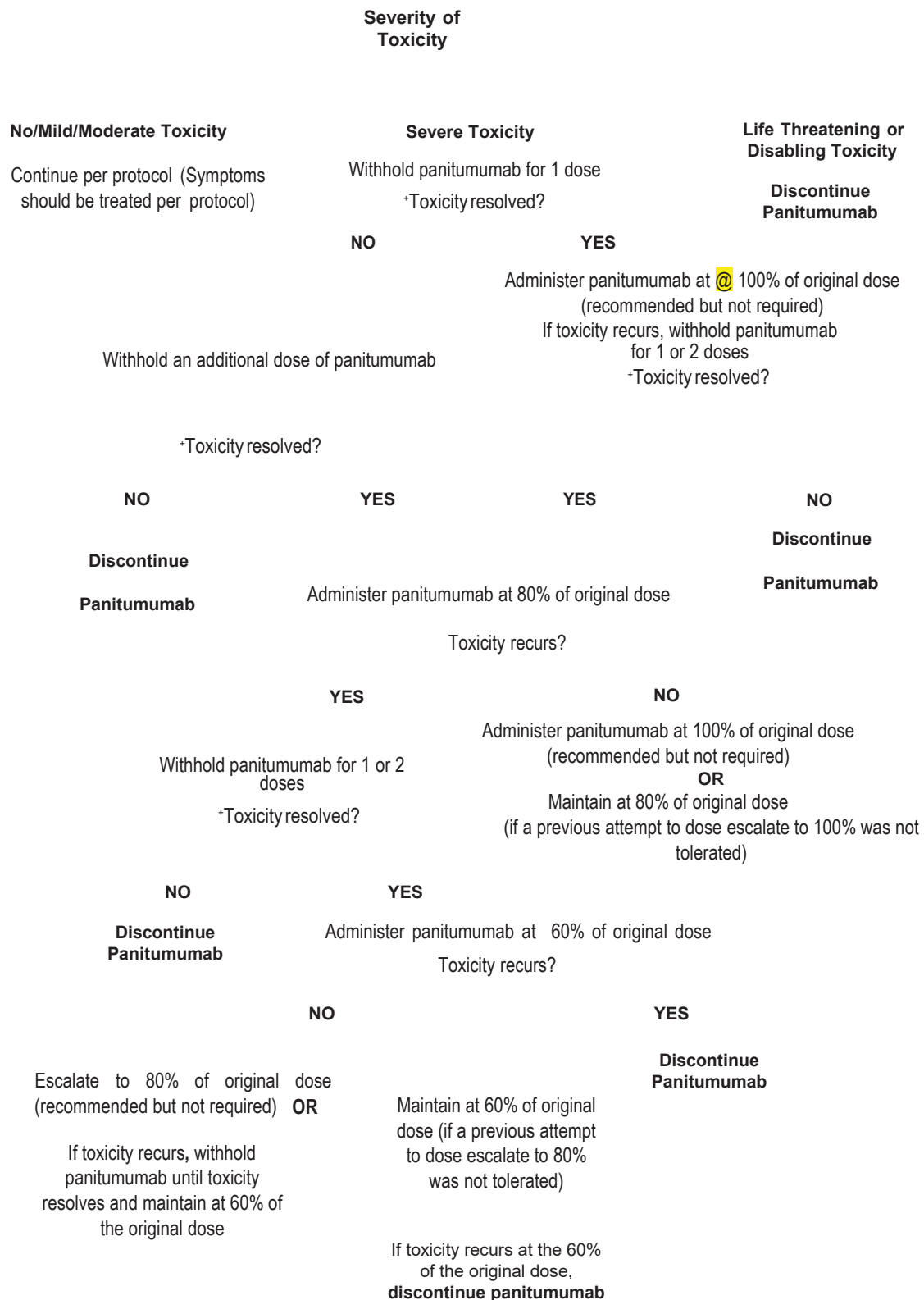
Subjects should be assessed for toxicity before each treatment cycle. Panitumumab, dose modification should be performed according to the schedule described below and outlined in Figure 1.

Panitumumab-related toxicity will be considered resolved if it improves to a degree that allows for re-treatment with panitumumab.

For subjects who experience a toxicity that meets the criteria for withholding a dose of panitumumab:

- Subjects receiving either 100% or 80% of the starting dose of panitumumab are allowed to have up to 2 subsequent doses withheld for toxicity. However a second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.
- Subjects treated at the 100% dose level, whose toxicity resolves after 1 dose of panitumumab is withheld, should be re-started at the 100% dose level (recommended but not required, reduction to the 80% dose is allowed as an alternative to re-challenge with the 100% dose).
- If toxicity recurs, subjects treated at the 100% dose or 80% dose should be restarted at the 80% dose or 60% dose, respectively, when the toxicity resolves after withholding 1 or 2 doses of panitumumab

Figure 1. Panitumumab Dose Modification Algorithm for Toxicity



If the chemotherapy is held or delayed for toxicity reasons, panitumumab should be delayed as well and will be resumed with the chemotherapy. This applies even if the toxicity is not related to panitumumab.

If treatment interruption is < 6 weeks from the previous cycle, and the subject has recovered from toxicity, as specified above, and the subject's disease has not progressed, treatment should be restarted at doses according to Tables 1, 2, 3, and 4. If treatment interruption is > 6 weeks, but the subject has recovered from toxicity and the subject's disease has not progressed, study team in conjunction with the investigator will determine the appropriateness of treatment resumption.

7.4 Warning and precautions

5-fluorouracil precautions

Diarrhea: 5-FU induce diarrhea. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement. If grade 2, 3 or 4 diarrhea occurs or has not resolved to grade ≤ 1 , administration of 5-FU should be delayed.

Hand-Foot Syndrome: 5-FU has been shown to cause hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema-erythema). If grade 2 or 3 hand-foot syndrome occurs, administration of 5-FU should be delayed until the event resolves or decreases in intensity to grade ≤ 1 .

Cardiotoxicity: There has been cardiotoxicity associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiograph changes. These adverse events may be more common in patients with a prior history of coronary artery disease.

Hepatic Insufficiency: In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when 5-FU is administered but no dose reduction is necessary. The effect of severe hepatic dysfunction on 5-FU is not known.

Hyperbilirubinemia: Administration of 5-FU should be interrupted if treatment related elevations in bilirubin of $>3.0 \times \text{ULN}$ (*grade 3*) or treatment-related elevations in hepatic aminotransferases (ALT, AST) of $>2.5 \times \text{ULN}$ occur. Treatment may be resumed when bilirubin decreases to $\leq 3.0 \times \text{ULN}$ (*grade 2*) or hepatic aminotransferases decrease to $\leq 2.5 \times \text{ULN}$.

Pregnancy: Female patients must be instructed to immediately inform the investigator. The Investigator should counsel the patient, and discuss the risk of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. The investigator should report all pregnancies in the study to the Sponsor.

Contraindications: 5-FU is contraindicated in patients with known hypersensitivity, in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy, and in patients with known DPD deficiency. 5-FU is contraindicated in patients with severe leukopenia, neutropenia, or thrombocytopenia, severe hepatic impairment, or severe renal impairment. Use of 5-FU is contraindicated during pregnancy and lactation, and concomitantly with sorivudine or its chemically related analogues, such as brivudine.

Oxaliplatin precautions

Peripheral neuropathy: oxaliplatin is associated with two types of peripheral neuropathy: paresthesias and dysesthesias of the hands and feet, and peri-oral region. The patients will be counseled to avoid cold drinks and exposure to cold water or air, especially for 3 to 5 days following oxaliplatin administration.

Laryngopharyngeal dysesthesias: an unusual laryngopharyngeal dysesthesia, a sensation of loss of breathing (acute respiratory distress) without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm), also has been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold.

Panitumumab precautions

Allergic/Hypersensitivity reactions: Allergic/hypersensitivity reactions may occur during or following the administration of panitumumab. However, prophylactic treatment with an antihistamine and a corticosteroid is not recommended. As a routine precaution, patients enrolled into this study should be observed closely for any potential AEs and a physician able to give emergency medical treatment must be present from the start of panitumumab infusion until at least 1 hour after the end of the infusion. The patient should be observed in an area with resuscitation equipment and other agents available (epinephrine, prednisolone equivalents etc). Should an allergic/hypersensitivity or infusion reaction to panitumumab occur, then the patient must be treated according to the best available medical practices. Grade 3 or 4 allergic/hypersensitivity reactions require immediate interruption of the infusion, appropriate medical measures and permanent discontinuation of treatment. Patients should be carefully monitored until the complete resolution of all signs and symptoms.

Skin reactions: The most common AE associated with panitumumab administration are skin reactions, particularly acne-like rash. If a patient experience a grade 3 skin reaction, panitumumab therapy must be interrupted for up to 2 consecutive weeks. Specific therapy is recommended according to local guidelines; Treatment may only be resumed if the reaction has resolved to grade 2 or less.

Interstitial pneumonitis: Severe interstitial pneumonitis has been described in subjects treated with the EGFR-pathway targeting therapy gefitinib. To date, no increased risk of interstitial pneumonitis has been identified with panitumumab. Nevertheless, all subjects must have adequate chest imaging prior to commencing cetuximab therapy in the study, as a safety precaution in order to document the baseline pulmonary condition. If there are respiratory symptoms at study entry, lung function tests and further diagnostic procedures must also be undertaken in order to diagnose pre-existing pulmonary fibrosis or interstitial pneumonitis. Furthermore, subjects will be regularly questioned about pulmonary symptoms during the study. Should pulmonary symptoms appear or worsen during or after panitumumab treatment, a detailed description is required and investigators should use their discretion in ordering such diagnostic procedures as are necessary to elicit an accurate diagnosis.

Electrolyte disturbances: Progressively decreasing serum magnesium levels have been observed leading to severe hypomagnesaemia in some patients. Hypomagnesaemia is reversible following discontinuation of panitumumab. Depending on severity, other electrolyte disturbances, mainly hypocalcaemia or hypercalcaemia, have also been observed. Determination of serum electrolyte levels is recommended prior to and periodically during panitumumab treatment. Electrolyte repletion is recommended, as appropriate.

7.5 Pre-emptive treatment of skin rash

Pre-emptive treatment of skin rash is mandatory and it must be administered from cycle one day one of study treatment.

It consists of:

- skin moisturizer applied to face, hands, feet, neck, back, and chest daily in the morning on rising;
- sunscreen (PABA free, SPF \geq 15, UVA and UVB protection) applied to exposed skin areas before going outdoors;
- topical steroid (1% hydrocortisone cream) applied to face, hands, feet, neck, back, and chest at bedtime
- Doxycycline 100 mg daily for one week starting from Day 1 of cycle 1 and then every other cycle. During the assumption of doxycycline, the patient must be advised to drink plenty of liquids to reduce the risk of esophageal irritation and ulceration; he/she must take doxycycline in upright position and must not lie down for an hour after taking the drug. The patient should not take iron supplements, multivitamins, calcium supplements, antacids, or laxatives within 2 hours before or

after taking doxycycline. Please remember that the absorption of tetracyclines is reduced when taken with foods, especially those which contain calcium.

7.6 Concomitant Treatments

All concomitant medications must be reported in the eCRF and include any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 28 days prior to Day 1 through the completion/early termination visit.

Allowed:

- a) Supportive treatment will be given as medically indicated; any concomitant medications must be specified in the Case Report Form
- b) Curative treatments are permitted: antiemetics, antiallergic measures
- c) Palliative radiotherapy may be given for control of pain or for other reasons without curative intent.
- d) Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.
- e) Hematopoietic growth factors (i.e., G-CSF or GM-CSF) may be used according to institutional or other specific guidelines (e.g., country, regional, or oncology organizations as ASCO, etc.) as primary or secondary prophylaxis. The use of any growth factor support must be documented in the patient's record. Growth factors must be discontinued at least 48 hours prior to initiation of the next cycle of chemotherapy. According to NCCN 2011 guidelines (www.nccn.org), erythropoiesis-stimulating agents (ESAs) may be considered for the treatment of cancer-related anemia in patients undergoing palliative treatment. Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia in cases where hemoglobin is < 11 g/dL or ≥ 2 g/dL below baseline, but only after the patient has been counseled about the risks and benefits of ESA use. The use of prophylactic medication such as Mg^{2+}/Ca^{2+} infusions or others for prevention of oxaliplatin-induced neuropathy is not recommended by this protocol, as their benefits have not been clearly established.
- f) Patients receiving bisphosphonates for a non-malignant indication are eligible for this study. Bisphosphonates or denosumab are acceptable for bone metastases if clinically indicated.
- g) Anticoagulation for maintenance of patency of permanent indwelling IV catheters is permitted.
- h) Pre-emptive skin treatment regimen is mandatory, if the patient is not allergic to tetracyclines.

Not permitted:

No other experimental or systemic anti-cancer therapy (approved or unapproved) is permitted during study treatment except for localized radiotherapy for pain control (provided that it does not compromise tumor assessments of target lesions).

Concomitant use of drugs with a potential ototoxic or nephrotoxic effect (e.g., aminoglycosides, cefalotine, furosemide, amphotericin B) should be avoided or adequately monitored.

The prevention of alopecia with a cold cap or of stomatitis with iced mouth rinse is not permitted because of the risk of triggering cold-related dysesthesias.

Live Vaccines: Vaccination with a live vaccine should be avoided in patients receiving 5-FU because of the potential for serious or fatal infections.

Allopurinol: Interactions with allopurinol have been observed with 5-FU, with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with 5-FU should be avoided.

Antivirals and Antiprotozoals: 5-FU should not be administered together with the antiviral drug sorivudine or its chemically related analogues, such as brivudine. A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of DPD by sorivudine, has been described in the literature (Diasio 1998). This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Metronidazole has been shown to increase the toxicity of 5-FU in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic (Martindale 2002). As it has been described in the literature, caution should be exercised.

Gastrointestinal Drugs: Pretreatment with cimetidine for 4 weeks led to increased plasma concentrations of 5-FU following IV and oral administration in 6 patients. The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow. No such effect was seen following single doses of cimetidine in 5 patients or pretreatment for just 1 week in 6 other patients. Care is required in patients taking both drugs simultaneously (Martindale 2002).

8.0 STUDY ASSESSMENTS

8.1 Description of Study Assessments

Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer treatments and procedures and history of weight loss), disease characteristics (histologic subtype and stage of disease), smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to randomization. Demographic data will include age, sex, and self-reported race/ethnicity.

Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressures while the patient is in a seated position.

Physical Examinations

At screening, a complete physical examination should include the evaluation of head, eye, ear, nose, and throat; cardiovascular; dermatological; musculoskeletal; respiratory; gastrointestinal; and neurological systems. Abnormalities identified at screening will be recorded as baseline conditions. Subsequent physical examinations will be symptom directed. Changes from baseline abnormalities should be assessed at each subsequent physical examination. New or worsening abnormalities should be recorded as adverse events if appropriate. As part of tumor assessments, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

ECOG Performance

ECOG performance status data and weight will be recorded at baseline and throughout the study.

Electrocardiogram (ECG)

An ECG is required at baseline. Additional ECGs may be performed during the study as clinically indicated. For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings.

Tumor and Response Evaluations

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be made by the investigator based on physical examinations, CT scans, or magnetic resonance imaging (MRI), using RECIST v 1.1. Within 28 days prior to randomization, the baseline disease assessment should include all areas of known and suspected disease through use of the most appropriate and reproducible radiological technique. Imaging may have been performed as part of standard of care prior to informed consent for this study. CT or MRI of the chest, abdomen, and pelvis should be performed using contrast media unless clinically contraindicated. CT scans of the neck should be included if clinically indicated. Bone scans (or focal X-ray) or brain imaging should be performed if metastatic disease is suspected. If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression prior to inclusion in the study. Evaluation of tumor response conforming to RECIST v1.1 must be documented every 8 weeks \pm 7 days during treatment until PD. Tumor assessments should be performed on this schedule regardless of whether study treatment has been administered or held, and also if the patient is off treatment due to reason other than PD (i.e. refusal or unacceptable toxicity).

Laboratory Assessments

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: White blood cell count with neutrophils, red blood cell count, hemoglobin, hematocrit and platelet count;
- Biochemistry: Bilirubin (total and direct), ASAT, ALAT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium, magnesium);
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at baseline. If clinically indicated, a urine test may be performed, but if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Patient-Reported Outcomes (PRO)

PRO data will be elicited from the patients in this study to more fully characterize the quality of life of patients. The following PRO instruments will be used, as shown in Appendix III:

- EORTC QLQ-C30 (Aaronson et al. 1993; Fayers and Bottomley 2002)

(see Appendix III)

- EORTC QLQ-CR29 (see Appendix III)
- EuroQol EQ-5D (Rabin and de Charro 2001) (see Appendix III)

The PRO instruments will be distributed by the study staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the administration of study treatment. PRO questionnaires should be performed every 8 weeks \pm 7 days during treatment until PD, regardless of whether study treatment has been administered or held, and also if the patient is off treatment due to reason other than PD (i.e. refusal or unacceptable toxicity).

8.2 Tumor Tissue Samples for Exploratory Biomarkers

As mandatory inclusion criteria, the tissue submitted will be used to assess exploratory biomarkers. The tissue submitted should be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen or 15 serial, freshly cut, unstained slides accompanied by an associated pathology report. Cytological samples are not acceptable.

A detailed description of tissue quality requirements and procedures for collection, handling, and shipping of the samples to the central laboratory will be provided in a separate laboratory manual.

Analysis on biomarkers is exploratory by nature and will be performed retrospectively after the main study analysis is completed. These assessments will be performed by the Sponsor at the Department of Pathology of Fondazione IRCCS Istituto Nazionale dei Tumori. The remaining tumor tissue block will be returned to the site upon request.

Tissue assessments will include testing of protein expression, activation status, somatic mutations, and/or gene amplification related to angiogenesis, tumorigenesis, inflammation, and other exploratory markers related to panitumumab and to colorectal cancer biology. Since the identification of new markers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of analyses remains to be determined; however, it will include the following tests:

- Next Generation sequencing (NGS) with With IonTorrent (Life-Technology, Applied Biosystem). "Hot-spot Cancer Panel", Personal Genome Machine. This panel analyses hotspot mutations in the following genes: ABL1; AKT1; ALK; APC; ATM; BRAF; CDH1; CDKN2A; CSF1R; CTNNB1; EGFR; ERBB2; ERBB4; EZH2; FBXW7; FGFR1; FGFR2; FGFR3; FLT3; GNA11; GNAQ; GNAS; HNF1A; HRAS; IDH1; IDH2; JAK2; JAK3; KDR (VEGFR2); KIT; KRAS; MET; MLH1; MPL; NOTCH1; NPM1; NRAS; PDGFRA; PIK3CA; PTEN; PTPN11; RB1; RET; SMAD4; SMARCB1; SMO; SRC; STK11; TP53; VHL.
- in-situ hybridization techniques to assess copy number variations in the following genes: EGFR, HER-2, HER-3, ALK, ROS1, RET, MET and IGF2.

8.3 Blood Samples for Exploratory Biomarkers

For consenting patients only, blood samples will be collected for exploratory research. In particular, samples will be collected at baseline, concomitantly with disease reassessment (every 8 weeks during both induction and maintenance phase) and at PD. If the patients goes off the study for unacceptable toxicity or treatment refusal, blood sample can still be collected until PD in consenting patients.

Samples will be sent to the Laboratory of Clinical Pharmacology of the Sponsor (Fondazione IRCCS Istituto Nazionale dei Tumori) for collection.

- In this study we will collect plasma samples in individual patients to analyze circulating tumor DNA by digital PCR (ddPCR) or next generation (NGS) approaches. Plasma samples analysis will be conducted also at the Molecular Oncology Laboratory of IRCCS – Candiolo Cancer Institute, Italy (Dr. Alberto Bardelli)
- Whole blood samples will also be collected only at baseline. In order to identify genetic factors associated to toxic effects on the skin, we plan to carry out pharmacogenetic analyses in all patients enrolled in the study. The potentially significant single nucleotide polymorphisms (SNPs), defined on the basis of gene involved in EGFR pathway and FOLFOX-4 chemotherapy will be genotyped after DNA extraction. Whole blood samples analysis will be conducted also at the Pharmacology Unit of L. Sacco University Hospital, Milan, Italy (Dr. Stefania Falvella)

Instruction manual will be provided for all peripheral laboratories. For sampling procedures, storage conditions and shipment instructions, see the laboratory manual.

9.0 SCHEDULE OF ASSESSMENT AND PROCEDURES

Written informed consent must be obtained prior to the patients undergoing any study-specific procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

For study flow chart see Appendix IV.

9.1 Screening and Baseline Assessments

The screening procedure may be started at any time within 4 weeks prior to treatment (day -28 to day 1), as follows:

- Assessment to be made within 28 days before treatment start: tumor assessment with imaging studies (abdomen CT/MRI plus chest CT); clinical assessment include: demographic data, medical history, cancer/treatment history, concomitant disease/treatment, physical examination, electrocardiogram (ECG); CEA determination and pregnancy test;
- Assessment to be made within 7 days before treatment start: height; weight; vital signs (blood pressure, pulse/heart rate); ECOG Performance Status; haematology; biochemistry. In consenting patients, also blood samples collection is to be performed.

9.2 Assessment during treatment

The following laboratory tests are to be done prior to any treatment cycle: haematology and biochemistry. Also, ECOG PS, vital signs, concomitant disease and treatment assessment, and toxicity evaluation are to be performed prior to any treatment cycle.

Tumor and response evaluation and PRO questionnaires are to be done every 8 weeks. In consenting patients, also blood samples collection is to be performed every 8 weeks.

9.3 Assessments at End of Treatment

At the end of treatment visit all of the followings need to be performed: haematology and biochemistry, ECOG PS, vital signs, tumor and response evaluation, concomitant disease and treatment assessment and toxicity evaluation. The visit at which a response assessment showed PD may be used as the end of treatment visit. In case of end of study due to PD, also PRO questionnaires (as well as, in consenting patients, blood samples collection) is to be done.

When a patient discontinues all study treatments, regardless of the reason for discontinuation, the patient will be asked to return to the clinic within 30 days (± 7 days), for toxicity evaluation.

9.4 Follow-Up Assessments

For patients with no progressive disease after terminating study treatment (i.e. treatment refusal or unacceptable toxicity), tumor assessments and PRO questionnaires (as well as, in consenting patients, blood samples collection) will be performed every 8 weeks until PD.

Data collection every 3 months will also include study treatment-related AEs (including serious AEs), subsequent anti-cancer therapies, and date of death. Survival follow-up ends with the death or loss to follow-up of the patient, or the Sponsor's decision to end the study.

10.0 PATIENT, STUDY, AND SITE DISCONTINUATION

10.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determination that it is in the best interest of the patient
- Patient non-compliance, specifically defined as missing two or more consecutive tumor assessments for unknown reasons, or receipt of non-protocol-specified anticancer treatment

10.2 Discontinuation from Study Drug

Patients must discontinue study drug treatment if they experience either of the following:

- Pregnancy
- Progressive disease

Patients who discontinue study drug before progressive disease is confirmed will be asked to return to the clinic for the end of treatment visit and should undergo follow-up assessments. The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prior to disease progression will not be replaced.

10.3 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

10.4 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study.

10.5 Replacement policy

Only patients included in the study that have not started treatment with the first dose of drugs will be replaced.

11.0 Safety

11.1 Adverse Events (or Adverse Experience)

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. AEs are graded according to Common Terminology Criteria for Adverse Events v4.03 (see Appendix II).

An AE 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 medicinal product, whether or not considered related to the medicinal product.

Due to regulatory requirements, events occurring during pre- and post-treatment periods should also be designated as AEs. Therefore, safety surveillance (reporting of AEs) commences at the time when the subject is enrolled into the study (date of signature of the informed consent) until the EOS visit has been performed. Therefore events occurring in the period between the signed informed consent and beginning of the study drug administration are to be designated as AEs. This procedure complies with requirements by some authorities.

11.2 Adverse drug reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out.

11.3 Serious adverse event or reaction/experience (SAE)

A serious AE (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Is a medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

The Principal Investigator or the Sub-Investigator must send immediately a report of all the SAEs, related or not to the study treatment. This must be done by email within 24 hours of the initial observation of the event on the provided SAE form, as highlighted in Appendix VI.

Other events to be treated as SAEs

Exposure to drug during pregnancy/lactation.

In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. The Investigator-Sponsor must be notified without delay and the subject followed during the entire course of the pregnancy and postpartum period. Prenatal and neonatal outcomes must be recorded even if they are completely normal and without AEs. Pregnancy cases must be notified also if a female partner of a male subject becomes pregnant during the male subject's participation in the study. The Serious Adverse Event Form (SAE report form) should be used,

even though pregnancy is not considered a SAE. On the AE CRF page the box seriousness "no" should be ticked.

Events not to be treated as SAEs

Progression of disease is not to be regarded as an AE; therefore, it is not a SAE. However, signs and symptoms of tumor progression may meet a criterion of a SAE and, if so, should be reported as such.

Death per se is an outcome and not regarded as SAE. The primary cause of death (the leading event to death) should be recorded and reported as SAE. "Died/fatal" will be reported as the outcome of the respective event. In case that no cause of death can be reported (e.g. unexplained death) the death per se might be reported as a SAE.

Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report form to Drug Safety, i.e.:

- Elective hospitalization and surgery for treatment of disease
- Elective hospitalization to simplify treatment or study procedures.

However, the events have to be entered in the adverse event section of the CRF

Methods of recording and assessing adverse events

All AEs must be documented in the appropriate section of the CRF. For SAEs a SAE report form (initial or follow-up) must be completed in addition.

The following aspects must be recorded for each event in the CRF:

A description of the AE in medical terms, not as reported by subject.

- The date of onset (start date).
- The date of recovery (stop date).
- The severity of the sign and/or symptom or clinically significant abnormal laboratory value according to NCI-CTCAE v.4.03. If no toxicity grade is described for a given sign, symptom or abnormal laboratory value, the investigator will grade the severity as mild (1), moderate (2), severe (3), or life-threatening or disabling (4).

Note: Death (grade 5) as defined by NCI-CTCAE v.4.03 is mainly regarded as an outcome and will be documented accordingly.

For each investigational product, the following should be recorded:

- Time of onset of the AE relative to the administration of the investigational product (if applicable)
- The causal relationship to each investigational product, as assessed by the investigator. One of the decisive factors in the decision is the temporal relation between the AE and the administration of the investigational product. The investigator must decide if there is a reasonable possibility that the investigational product was the cause of the AE. The question, "Is this AE suspected to be reasonably related to the investigational product?" will be answered "NO (not related)" or "YES (related)", where "related" is defined to mean that the AE could medically (pharmacologically or clinically) be attributed to the investigational product under study in this protocol.

Action:

- No change
- Reduction of infusion rate
- Dose reduction
- Temporary discontinuation
- Permanent discontinuation
- Not applicable

The outcome according to the following definitions:

- Recovered (AE disappeared)
- Recovered with sequelae (AE has resulted in permanent disability/incapacity)
- Not yet recovered

- Not recovered at death
- Change in toxicity grade/severity or seriousness (e.g., an AE with no change of toxicity grade but newly classified as a SAE due to hospitalization)
- Fatal (AE resulted in death)

In presence of seriousness the corresponding serious criteria must be ticked:

- Subject died
- Life-threatening
- New or prolonged hospitalization
- Persistent/significant disability
- Congenital abnormality
- Important medical event

Leading event: for SAEs only, it must be reported whether the SAE is the leading event (i.e., the primary medical reason for SAE reporting)

If in any subject the same AEs occurs on several occasions, then the AE in question must be documented and assessed anew each time.

Only abnormal laboratory values that are deemed clinically significant by the investigator will be documented in the AE section of the CRF. Any laboratory parameters that are outside the normal range and are significantly different from the baseline values will be followed up as necessary until the abnormality has been resolved or the etiology clarified to the investigator's satisfaction.

12.0 Data collection and management

12.1 Data quality assurance

The Trial Office of Fondazione IRCCS Istituto Nazionale dei Tumori will develop electronic eCRF specific for this study. The Sponsor Fondazione IRCCS Istituto Nazionale dei Tumori will be responsible for data management of this study, including quality checking of the data.

Data entered manually will be collected using eCRFs. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the system.

eCRFs and correction documentation will be maintained in the system's audit trail.

System backups for data and records retention for the study data will be consistent with standard procedures.

12.2 Electronic Case Report Forms (eCRFs)

eCRFs are to be completed using a Sponsor-designated system for this study. Sites will receive training and have access for appropriate eCRF completion. For each patient enrolled, an electronic Case Report Form (eCRF) must be completed and signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the pre-randomization screening.

12.3 Source data documentation

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents. Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a

clinical trial. Not necessarily all sites will be monitored: site selection and monitoring frequency will be evaluated during the study, depending on recruitment, number of discrepancies and in the case of site problems. Also remote monitoring will be planned if applicable.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 12.4. To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

12.4 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF. The NCI CTCAE (v4.03) grading scale will be used for assessing adverse event severity (Appendix II). After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events, regardless of relationship to studydrug, will be reported until 28 days after the last dose of study drug. After this period, any AE that occurs in the course of a clinical study and is considered to be related to the IMP must be monitored and followed up until the outcome is known, whenever possible. There must be documented reasonable attempts to obtain this information. It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed.

12.5 Procedure for reporting serious adverse events

The Principal Investigator or the Sub-Investigator must send immediately a report of all the SAEs, related or not to the study treatment. This must be done by email within 24 hours of the initial observation of the event on the provided SAE form, as highlighted in Appendix VI. The SAE form must be emailed to the Institutional address of the Sponsor:
farmacovigilanza.studispontanei@istitutotumori.mi.it

All SAEs occurring during the treatment period and within 30 days after the last protocol treatment, must be reported to the safety desk. Any late serious adverse drug reaction (SADR), occurring after this 30-day period, should follow the same reporting procedure. The investigator will decide if these events are related to the study treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the SAE forms (Appendix VI).

The Sponsor will be responsible for safety reporting to Regulatory Authorities according to the current laws.

The Sponsor will provide Amgen with a copy of any SAE report received by the Investigators. The Sponsor will send the SAE forms to Amgen Safety to the following fax number: 800916570 (in case of any issues with the fax number or for any other question the following e-mail address: eu-it-farmacovigilanza@amgen.com must be used).

All SAEs must be forwarded to Amgen as soon as possible, but no later than 1 business day of Sponsor awareness; a copy of SUSARs must be sent to Amgen at time of regulatory submission. Pregnancy and Lactation reports must be sent within 10 days of Sponsor awareness.

The Sponsor will also provide Amgen with an Annual Safety Report and with a copy of any other communication or aggregate report, containing safety data generated during the course of the study, sent to the Regulatory Authorities by the Sponsor. The final study report should be sent to Amgen no later than 1 calendar year of study completion.

12.6 Retention of Records

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO questionnaires, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

13.0 STATISTICAL CONSIDERATIONS

13.1 Sample size calculation

It is planned to enroll 224 patients, 112 in the control group and 112 in the study group, over a two-year period.

The sample size is calculated on the basis of a non-inferiority hypothesis of median PFS with panitumumab alone as compared to 5-fluorouracil/leucovorin and panitumumab, taking into account a median PFS of 10 months observed in the PRIME trial. An overall sample size of 224 subjects (112 in the control group and 112 in the study group) achieves 90% power to detect a probability of 50% in the control group and a maximum difference of 15% in the study group, with a significance level of 0.1. The drop-out rate is 15%. Equal 1:1 allocation ratio in the two trial arms is planned, and the patient accrual pattern over time is foreseen to be uniform.

13.2 Analysis Of Efficacy

Intent-to-treat Population: All patients that were included in the trial by signing the informed consent and assigned a study patient number (randomized patients).

Per Protocol Population: All patients will be excluded from the per-protocol analysis who:

- did not receive a minimum of 16 weeks of treatment and started the maintenance treatment phase.
- severely violated protocol inclusion or exclusion criteria

Demographic and baseline characteristics such as age, sex, race, and baseline disease characteristics will be summarized by treatment arm for the ITT population. Descriptive baseline summaries of continuous data will present mean, standard deviation, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

13.3 PFS and OS analysis

Definitions of efficacy study endpoints and criteria for the quantification of PFS and OS in particular are provided in section 6.3.

Descriptive analysis of PFS will be carried out by plotting Kaplan–Meier survival curves, and median survival will be estimated. As typically done for studies of this type, non-inferiority of experimental treatment toward control will be established in case of the confidence interval margin of PFS difference not overlapping the inferiority margin. An additional analysis will be conducted by mean of the Cox proportional hazard regression model, incorporating information on recognized prognostic factors so as to obtain an adjusted estimate of experimental treatment effect. Similar analyses will be conducted on OS.

All efficacy analyses will be primarily based on the intent-to-treat population, and further verified on the per-protocol population.

13.4 Patient-reported outcome analysis

The analysis of PRO (assessed using the EORTC QLQ-C30, the EORTC QLQ-CR29 and the EuroQol EQ-5D questionnaires) will be performed according to the EORTC Scoring and Reference Values Manual. All scores and subscales will be assessed through descriptive summary statistics.

13.5 Handling of missing data

For PFS, patients without a date of disease progression will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at day 1. For OS, patients who are not reported as being died will be analyzed as censored observations on the date when they were last known to be alive. If no post-baseline data are available, OS will be censored at day 1.

13.6 Analysis of safety and safety population

Patients not receiving at least one dose of study drug will be excluded from the analysis of safety. Tables of adverse event incidence and individual incidence will be produced according to the primary system-organ class (SOC) and within the category defined in the CTCAE v4.03. The summaries will be overall (severity grades 1-5) and for grade ≥ 3 events. Multiple occurrences of the same event will be counted once at the maximum severity. A complementary analysis of adverse events by severity of event and by relationship to trial treatment will also be performed. Will report the actions taken in terms of treatment discontinuation. A standard safety analysis with tables and shift tables for laboratory data will be provided. Vital signs, coded as clinically normal or abnormal, will be described.

Similar summaries will be made for serious adverse events.

Description of dosage incidents, hospitalizations and premature withdrawals will be provided.

14.0 Ethical Considerations

14.1 Compliance with regulations

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

14.2 Informed consent

Sponsor's sample Informed Consent Form will be provided to each site. Each Site can modify the template provided, but the Sponsor must review and approve any proposed deviations from the sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission.

Regarding specific Informed Consent(s) on exploratory biomarkers, the investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

14.3 Confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in any of the study data sets. Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law. Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes. Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, Sponsor's monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

15.0 References

1. Global cancer statistics. *Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D.* *CA Cancer J Clin.* 2011 Mar-Apr;61(2):69-90. doi: 10.3322/caac.20107. Epub 2011 Feb 4. Erratum in: *CA Cancer J Clin.* 2011 Mar-Apr;61(2):134. PMID: 21296855 [PubMed - indexed for MEDLINE]
2. Worldwide variations in colorectal cancer. *Center MM, Jemal A, Smith RA, Ward E.* *CA Cancer J Clin.* 2009 Nov-Dec;59(6):366-78. doi: 10.3322/caac.20038. Review. PMID: 19897840 [PubMed - indexed for MEDLINE]
3. The continuum of care: a paradigm for the management of metastatic colorectal cancer. *Goldberg RM, Rothenberg ML, Van Cutsem E, Benson AB 3rd, Blanke CD, Diasio RB, Grothey A, Lenz HJ, Meropol NJ, Ramanathan RK, Becerra CH, Wickham R, Armstrong D, Viele C.* *Oncologist.* 2007 Jan;12(1):38-50. Review. PMID: 17227899 [PubMed - indexed for MEDLINE]
4. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *de Gramont A, Bosset JF, Milan C, Rougier P, Bouché O, Etienne PL, Morvan F, Louvet C, Guillot T, François E, Bedenne L.* *J Clin Oncol.* 1997 Feb;15(2):808-15. PMID: 9053508 [PubMed - indexed for MEDLINE]
5. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A.* *J Clin Oncol.* 2004 Jan 15;22(2):229-37. Epub 2003 Dec 2.
6. Colorectal cancer. *Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N.* *Lancet.* 2010 Mar 20;375(9719):1030-47. doi: 10.1016/S0140-6736(10)60353-4. Review. PMID: 20304247
7. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J.* *J Clin Oncol.* 2010 Nov 1;28(31):4697-705. doi: 10.1200/JCO.2009.27.4860. Epub 2010 Oct 4. PMID: 20921465 [PubMed - indexed for MEDLINE]
8. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Williams R, Rong A, Wietorek J, Sidhu R, Patterson SD.* *N Engl J Med.* 2013 Sep 12;369(11):1023-34. doi: 10.1056/NEJMoa1305275. PMID: 24024839 [PubMed - indexed for MEDLINE]
9. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. *Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA, Karapetis CS.* *Ann Oncol.* 2014 Aug 12. pii: mdu378. [Epub ahead of print] Review. PMID: 25115304 [PubMed - as supplied by publisher]
10. Abstract 5010 - CALGB/SWOG 80405: PHASE III trial of irinotecan/5 FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded ras analyses untreated metastatic adenocarcinoma of the colon or rectum (MCRC) *A.P. Venook et al* *Annals of Oncology* (2014) 25 (suppl_2): ii105-ii117. 10.1093/annonc/mdu193
11. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moehler M,*

- Lindig RU, Modest DP, Rossius L, Kirchner T, Jung A, Stintzing S.* Lancet Oncol. 2014 Sep;15(10):1065-75. doi: 10.1016/S1470-2045(14)70330-4. Epub 2014 Jul 31. PMID: 25088940 [PubMed - in process]
12. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, Yu H, Oliner KS, Go WY. J Clin Oncol. 2014 Jul 20;32(21):2240-7. doi: 10.1200/JCO.2013.53.2473. Epub 2014 Mar 31. PMID: 24687833 [PubMed - indexed for MEDLINE]
 13. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer--a GERCOR study. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, André T, Tabah-Fisch I, de Gramont A. J Clin Oncol. 2006 Jan 20;24(3):394-400. PMID: 16421419 [PubMed - indexed for MEDLINE]
 14. Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC). Miriam Koopman, Lieke Simkens, Anne Maria May, Linda Mol, Harm van Tinteren, Cornelis J. A. Punt J Clin Oncol 32:5s, 2014 (suppl; abstr 3504)
 15. Maintenance strategy with fluoropyrimidines (FP) plus Bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A phase III non-inferiority trial (AIO KRK 0207). Dirk Arnold et al J Clin Oncol 32:5s, 2014 (suppl; abstr 3503^)
 16. 4990 - Phase II study of first-line mFOLFOX plus cetuximab (C) for 8 cycles followed by mFOLFOX plus C or single agent (s/a) C as maintenance therapy in patients (p) with metastatic colorectal cancer (mCRC): the MACRO-2 trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]) P. García Alfonso et al Annals of Oncology (2014) 25 (suppl_4): iv167-iv209. 10.1093/annonc/mdu333
 17. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. Díaz-Rubio E, Gómez-España A, Massutí B, Sastre J, Abad A, Valladares M, Rivera F, Safont MJ, Martínez de Prado P, Gallén M, González E, Marcuello E, Benavides M, Fernández-Martos C, Losa F, Escudero P, Arrivi A, Cervantes A, Dueñas R, López-Ladrón A, Lacasta A, Llanos M, Tabernero JM, Antón A, Aranda E; Spanish Cooperative Group for the Treatment of Digestive Tumors. Oncologist. 2012;17(1):15-25. doi: 10.1634/theoncologist.2011-0249. Epub 2012 Jan 10. PMID: 22234633 [PubMed - indexed for MEDLINE]
 18. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eisenhauer EA, Therasse P, Bogaerts J, et al. Eur J Cancer 2009; 45(2):228-47.

APPENDIX I

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

ECOG Scale	Performance Status
0	Fully active, able to carry out all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completed disabled. Cannot carry out any selfcare. Totally confined to bed or chair.
5	Dead

NOTE THAT:

ECOG 0 corresponds to Karnofsky performance status of	100-90
ECOG 1 corresponds to Karnofsky performance status of	80-70
ECOG 2 corresponds to Karnofsky performance status of	60-50
ECOG 3 corresponds to Karnofsky performance status of	40-30
ECOG 4 corresponds to Karnofsky performance status of	20-10
ECOG 5 corresponds to Karnofsky performance status of	0

APPENDIX II

NCI Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Publish Date: May 28, 2009 (v4.03: June 14, 2010)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

The CTCAE v4.0 manual can be found at the following URL:
<http://ctep.cancer.gov/reporting/ctc.html>

APPENDIX III - Patients Reported Outcomes

ITALIAN



EORTC QLQ-C30 (version 3.0)

Con questo questionario vorremmo sapere alcune cose su di Lei e sulla Sua salute. La preghiamo di rispondere a tutte le domande ponendo un cerchio attorno al numero che meglio corrisponde alla Sua risposta. Non esiste una risposta "giusta" o "sbagliata". Le Sue informazioni verranno tenute strettamente riservate.

Per favore scriva solo le iniziali del Suo nome e cognome:

--	--	--	--	--	--	--	--	--	--

Data di nascita (g, m, a):

--	--	--	--	--	--	--	--	--	--

La data di oggi (g, m, a):

31

--	--	--	--	--	--	--	--	--	--

	No	Un po'	Parecchio	Moltissimo
1. Ha difficoltà nel fare lavori faticosi, come sollevare una borsa della spesa pesante o una valigia?	1	2	3	4
2. Ha difficoltà nel fare una <u>lunga</u> passeggiata?	1	2	3	4
3. Ha difficoltà nel fare una <u>breve</u> passeggiata fuori casa?	1	2	3	4
4. Ha bisogno di stare a letto o su una sedia durante il giorno?	1	2	3	4
5. Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?	1	2	3	4

Durante gli ultimi sette giorni:

	No	Un po'	Parecchio	Moltissimo
6. Ha avuto limitazioni nel fare il Suo lavoro o i lavori di casa?	1	2	3	4
7. Ha avuto limitazioni nel praticare i Suoi passatempi-hobby o altre attività di divertimento o svago?	1	2	3	4
8. Le è mancato il fiato?	1	2	3	4
9. Ha avuto dolore?	1	2	3	4
10. Ha avuto bisogno di riposo?	1	2	3	4
11. Ha avuto difficoltà a dormire?	1	2	3	4
12. Ha sentito debolezza?	1	2	3	4
13. Le è mancato l'appetito?	1	2	3	4
14. Ha avuto un senso di nausea?	1	2	3	4
15. Ha vomitato?	1	2	3	4

[Continuare alla pagina successiva](#)



EORTC QLQ – CR29

Talvolta i pazienti accusano i seguenti sintomi. La preghiamo di indicare il grado con cui ha provato questi sintomi durante gli ultimi sette giorni. Risponda tracciando un cerchio intorno al numero che meglio definisce la Sua situazione.

Durante la settimana scorsa:	No	Un po'	Parecchio	Moltissimo
31. Ha urinato spesso durante il giorno?	1	2	3	4
32. Ha urinato spesso durante la notte?	1	2	3	4
33. Ha subito una perdita involontaria di urina?	1	2	3	4
34. Ha provato dolore nell'urinare?	1	2	3	4
35. Ha provato dolore addominale?	1	2	3	4
36. Ha provato dolori alle natiche o alla zona dell'ano o del retto?	1	2	3	4
37. Ha avvertito una sensazione di gonfiore all'addome?	1	2	3	4
38. Ha trovato sangue nelle feci?	1	2	3	4
39. Ha trovato muco nelle feci?	1	2	3	4
40. Ha provato secchezza alla bocca?	1	2	3	4
41. Ha perduto i capelli in seguito alla terapia?	1	2	3	4
42. Ha riscontrato problemi con il senso del gusto?	1	2	3	4

Durante la settimana scorsa:	No	Un po'	Parecchio	Moltissimo
43. Ha avuto preoccupazioni per la Sua salute futura?	1	2	3	4
44. Ha avuto preoccupazioni riguardo al peso?	1	2	3	4
45. Si è sentito/a fisicamente meno attraente in conseguenza della malattia o della terapia?	1	2	3	4
46. Si è sentito/a meno virile/femminile in conseguenza della malattia o della terapia?	1	2	3	4
47. Si è sentito/a insoddisfatto/a del Suo corpo?	1	2	3	4
48. Ha una sacca per stomia (colostomia/ileostomia)? (cerchiare la risposta corretta)	Si		No	

Continuare alla pagina successiva

Durante la settimana scorsa:

No Un-
po' Parec-
chio Multis-
simo

<u>Rispondere a queste domande SOLO SE SI UTILIZZA UNA SACCA PER STOMIA. altrimenti passare oltre:</u>				
49. Ha riscontrato perdite involontarie di gas o flatulenze dalla sacca per stomia?	1	2	3	4
50. Ha riscontrato perdite di feci dalla sacca per stomia?	1	2	3	4
51. La pelle intorno allo stoma si è irritata?	1	2	3	4
52. Ha dovuto cambiare la sacca molto spesso durante il giorno?	1	2	3	4
53. Ha dovuto cambiare la sacca molto spesso durante la notte?	1	2	3	4
54. Ha provato imbarazzo riguardo allo stoma?	1	2	3	4
55. Ha avuto problemi nell'occuparsi della sacca per stomia?	1	2	3	4

Rispondere a queste domande SOLO SE NON SI UTILIZZA UNA SACCA PER STOMIA:

49. Ha riscontrato perdite involontarie di gas o flatulenze dall'ano?	1	2	3	4
50. Ha riscontrato perdite di feci dall'ano?	1	2	3	4
51. La pelle intorno all'ano si è irritata?	1	2	3	4
52. È andato/a spesso di corpo durante il giorno?	1	2	3	4
53. È andato/a spesso di corpo durante la notte?	1	2	3	4
54. Ha provato imbarazzo nell'andare di corpo?	1	2	3	4

Durante le ultime 4 settimane:

No Un-
po' Parec-
chio Multis-
simo

<u>Solo per gli uomini:</u>				
56. In che misura ha provato interesse per il sesso?	1	2	3	4
57. Ha incontrato difficoltà a ottenere o mantenere un'erezione?	1	2	3	4

<u>Solo per le donne:</u>				
58. In che misura ha provato interesse per il sesso?	1	2	3	4
59. Ha provato dolore o fastidio durante il rapporto sessuale?	1	2	3	4



Questionario sulla Salute

Versione italiana per l'Italia

(Italian version for Italy)

Sotto ciascun argomento, faccia una crocetta sulla casella (UNA SOLA) che descrive meglio la sua salute OGGI.

CAPACITÀ DI MOVIMENTO

- Non ho difficoltà nel camminare
- Ho lievi difficoltà nel camminare
- Ho moderate difficoltà nel camminare
- Ho gravi difficoltà nel camminare
- Non sono in grado di camminare

CURA DELLA PERSONA

- Non ho difficoltà nel lavarmi o vestirmi
- Ho lievi difficoltà nel lavarmi o vestirmi
- Ho moderate difficoltà nel lavarmi o vestirmi
- Ho gravi difficoltà nel lavarmi o vestirmi
- Non sono in grado di lavarmi o vestirmi

ATTIVITÀ ABITUALI (per es. lavoro, studio, lavori domestici, attività familiari o di svago)

- Non ho difficoltà nello svolgimento delle attività abituali
- Ho lievi difficoltà nello svolgimento delle attività abituali
- Ho moderate difficoltà nello svolgimento delle attività abituali
- Ho gravi difficoltà nello svolgimento delle attività abituali
- Non sono in grado di svolgere le mie attività abituali

DOLORE O FASTIDIO

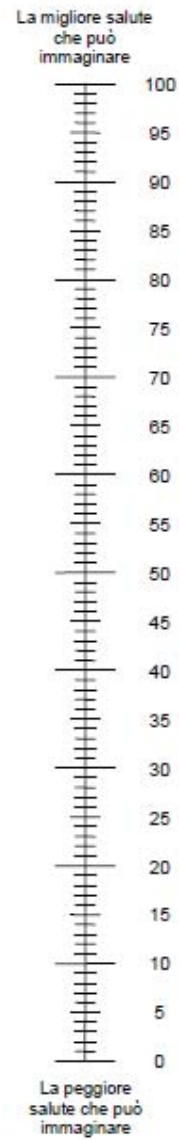
- Non provo alcun dolore o fastidio
- Provo lieve dolore o fastidio
- Provo moderato dolore o fastidio
- Provo grave dolore o fastidio
- Provo estremo dolore o fastidio

ANSIA O DEPRESSIONE

- Non sono ansioso/a o depresso/a
- Sono lievemente ansioso/a o depresso/a
- Sono moderatamente ansioso/a o depresso/a
- Sono gravemente ansioso/a o depresso/a
- Sono estremamente ansioso/a o depresso/a

- Vorremmo sapere quanto è buona o cattiva la sua salute OGGI.
- Questa è una scala numerata che va da 0 a 100.
- 100 rappresenta la migliore salute che può immaginare. 0 rappresenta la peggiore salute che può immaginare.
- Segni una X sul punto della scala per indicare com'è la sua salute OGGI.
- Poi, scriva nella casella qui sotto il numero che ha segnato sulla scala numerata.

LA SUA SALUTE OGGI =



APPENDIX IV: FLOW CHART OF EXAMINATIONS

Parameters	Baseline	Induction Treatment	Maintenance Treatment	End of Treatment	Follow up
		Every 2 weeks	Every 2 weeks Until PD		Every 3 months
ARM A		FOLFOX-4 panitumumab	5-FU/LV Panitumumab		
ARM B			Panitumumab		
Informed consent	X ⁴				
Medical history	X ⁴				
Physical examination and vital signs	X ³	X	X	X	X
ECOG PS	X ³	X	X	X	X
Concomitant diseases and treatments	X ⁴	X	X	X	
Toxicity evaluation		X	X	X ⁷	
ECG	X ⁴	If clinically indicated			
Hematology ¹	X ³	X	X	X	
Blood chemistry ²	X ³	X	X	X	
Pregnancy test ⁸	X ⁴	If clinically indicated			
Chest/Abdomen CT or Abdomen MRI CEA	X ⁴	X ^{5,6}	X ^{5,6}		
Tissue block collection	X				
Blood samples collection ¹⁰	X ³	X ⁶	X ⁶	X ⁶	
Patient reported outcomes (PRA) ⁹	X	X ⁶	X ⁶	X ⁶	

1. White blood cell count with neutrophils, red blood cell count, hemoglobin, hematocrit and platelet count
2. Bilirubin (total and direct), ASAT, ALAT, alkaline phosphatase, albumin, LDH, serum creatinine, glucose, electrolytes (sodium, potassium, calcium, magnesium).
3. Up to 7 days before starting of treatment
4. Up to 28 days before starting of treatment
5. Using the same technique performed at baseline
6. Every 4 cycles (8 weeks)
7. Follow up on any unresolved adverse events 28 days after last drugs intake
8. All women of childbearing potential (including those who have had a tubal ligation) will have a pregnancy test at baseline and if clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
9. PRA will be assessed with specific questionnaires (EuroQoL EQ-5D, EORTC QLQ-C30, EORTC QLQ-CR29)
10. Optional, specific informed consent to be signed by the patient

APPENDIX V

ADVERSE EVENT REPORT FORM

Instructions for completing the “SAE/ER from a Clinical Trial” form

The “SAE/ER from a Clinical Trial” (SAE = serious adverse event, ER = expedited report) form is used by the Investigator to report cases involving SAEs, alert terms and “significant overdoses” to the sponsor.

1. Serious Adverse Events

General: All serious adverse events which occur during this study, whether or not considered to be associated with the study medication must be reported immediately by phone and fax to the Study Manager, Study Monitor or Clinical Research Associate.

Make sure that in parallel you fill in an AE form in the study book for adverse event, which complies with the definition of serious adverse event. Make sure you give the same information in both documents.

One “SAE/ER from a Clinical Trial” form must be completed for each serious event. The form must be used for the initial report of the serious adverse event and for the follow-up report(s) concerning this event.

A follow-up report including all new information on the event must be prepared using a second copy of this form. This report is either to be sent to: farmacovigilanza.studispontanei@istitutotumori.mi.it

Definition of a SAE: A serious adverse event is one that at any dose:

- Results in death
- Is life-threatening¹
- Requires inpatient hospitalization or prolongs hospitalization
- Results in persistent or significant disability/incapacity²
- Involves congenital anomaly/birth defect
- Is medically important³

¹ This term means that the patient was at immediate risk of death at the time of the AE; it does not refer to an AE which hypothetically might have caused death if it were more serious.

² This term means that there is a substantial disruption of a person's ability to carry out normal life functions.

³ Medical and scientific judgment should be exercised in deciding whether other AEs may be considered serious because they jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Cases involving cancer, as an AE should be reported as serious using the criterion medically important.

Adverse events, which do not fall into the above categories, are defined as non-serious.

Cases of overdose with an AE that meets one of the criteria given above should of course be reported as serious.

LOT NUMBER:					<input type="checkbox"/> NA	<input type="checkbox"/> NA
C)				From: To:	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> YES <input type="checkbox"/> NO
LOT NUMBER:					<input type="checkbox"/> NA	<input type="checkbox"/> NA

24. IS THE SAE LIKELY TO BE A REACTION TO ONE OF THE DRUGS IN THE TRIAL?	A) <input type="checkbox"/> YES	<input type="checkbox"/> NO
	B) <input type="checkbox"/> YES	<input type="checkbox"/> NO
	C) <input type="checkbox"/> YES	<input type="checkbox"/> NO
24a. IF YES, IS THE REACTION UNEXPECTED?	A) <input type="checkbox"/> YES	<input type="checkbox"/> NO
	B) <input type="checkbox"/> YES	<input type="checkbox"/> NO
	C) <input type="checkbox"/> YES	<input type="checkbox"/> NO

III. CONCOMITANT DRUG(S) AND HISTORY

25. CONCOMITANT DRUGS (if known: doses,route of administration,indication for use,therapy dates...)

26. OTHER RELEVANT HISTORY (e.g. diseases, allergies, pregnancy with last month of period, etc.)

IV. REPORTER INFORMATION

27. NAME ,ADDRESS,PHONE OF REPORTER		27a.COUNTRY: ITALY
27b. DATE OF THIS REPORT <i> / /</i> <i>dd/mm/yyyy</i>	27c. REPORTER SIGNATURE	27d.REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> HEALTH PROFESSIONAL
28 REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP	29.DATE RECEIVED BY PHARMACOVIGILANCE INT SERVICE:	

30. ADDITIONAL INFORMATIONS AND/OR FOLLOW UP:

GUIDA ALLA COMPILAZIONE DEL SAE FORM

-Inserire il nome del protocollo cui fa riferimento il SAE

1 inserire le iniziali del soggetto (campo obbligatorio)

1a inserire il numero random del soggetto

2 inserire la data di nascita♦

2a inserire l'età del soggetto♦

♦Uno dei campi 2 o 2a de essere compilato (campo obbligatorio)

3 sesso del soggetto (campo obbligatorio)

4-6 data in cui è comparso il SAE (campo obbligatorio)

7 indicare l'etnia del soggetto

8 descrizione dell'evento avverso , con eventuale inserimento dei dati di esami di laboratorio correlati all'evento (campo obbligatorio)

9-14 tipologia del SAE (campo obbligatorio)

15 azioni intraprese in seguito alla comparsa del SAE

16 esito del SAE

17 farmaco/farmaci sospetti:indicare il principio attivo o il nome commerciale o l'acronimo e il numero di lotto (campo obbligatorio)

18 indicare la dose giornaliera o prevista ad ogni singola somministrazione (campo obbligatorio)

19 indicare la via di somministrazione (campo obbligatorio)

20 indicare il motivo di utilizzo del farmaco/farmaci (campo obbligatorio)

21 indicare la data di inizio e la data in cui è terminata la terapia con tale farmaco (campo obbligatorio)

22 indicare se l'evento si è risolto dopo l'eventuale sospensione del farmaco

23 indicare se l'evento si è ripresentato all'eventuale reintroduzione del farmaco

24 indicare se si ritiene che vi sia un nesso di causalità tra il SAE e il farmaco (campo obbligatorio)

24 a in caso affermativo al punto 24 indicare se la reazione è inattesa

25 indicare tutti i farmaci assunti dal soggetto nel periodo di utilizzo del farmaco sospetto. Specificando almeno principio attivo o nome commerciale e se conosciute tutte le altre informazioni correlate (dose giornaliera, via di somministrazione, motivo di utilizzo, durata della terapia)

26 indicare tutte le patologie del soggetto, specificando anche eventuali allergie, se fumatore, interventi pregressi, ecc..

27 nome e cognome e indirizzo della struttura del segnalatore (campo obbligatorio)

27a Stato del segnalatore (ITALY: campo già precompilato)

27b data in cui si effettua la segnalazione (campo obbligatorio)

27c firma del segnalatore (campo obbligatorio)

27d fonte della segnalazione (STUDY, HEALTH PROFESSIONAL campo già precompilato)

28 indicare il tipo di report: se primo invio o derivato da un follow up/aggiornamento di SAE segnalato in precedenza

29 data in cui la segnalazione viene ricevuta dall'INT (a cura del responsabile di farmacovigilanza)

30 campo dedicato a qualsiasi informazione il segnalatore ritenga importante riportare o aggiornamenti di follow up del caso

APPENDIX VII

DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably

in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.