AIO *Study KRK 0107* *in cooperation with* Arbeitskreis Klinische Studien

Phase II Study:

An Open-label Randomized Phase II Study of Panitumumab Plus Oral Capecitabine and Infusional Oxaliplatin (XELOX) or XELOX alone for Second-line Treatment of Patients with Metastatic Colorectal Cancer (VOXEL Study)

EudraCT Nr.: 2007-004866-42
ClinicalTrial.gov Nr.: NCT00950820

Final Study Report • January 2012

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1 STUDY SYNOPSIS

Title

An Open-label Randomized Phase II Study of Panitumumab Plus Oral Capecitabine and Infusional Oxaliplatin (XELOX) or XELOX alone for Second-line Treatment of Patients with Metastatic Colorectal Cancer (VOXEL-Study)

Study Phase

II

Indication

Metastatic colorectal cancer (mCRC)

Estimated Study Duration

Recruitment phase:	24 month
Duration of treatment:	approximately 6 months
Follow-up phase:	6 month after the last patient stopped treatment (incl. a 56 day safety follow-up)
Estimated end of the study:	October 2012 (cf. section **Actual study course**)

Primary Objective

To assess the differences in progression-free survival at 6 months in subjects with KRAS wild-type metastatic colorectal cancer receiving second line treatment (after failure of a previous irinotecan and 5FU based regimen) with panitumumab plus XELOX compared to the treatment with XELOX alone, without major safety problems.

Secondary Objectives

To assess that, for subjects with KRAS wild-type metastatic colorectal cancer, objective response rate (ORR), disease control rate (DCR), duration of response (DOR), time to progression (TTP), duration of stable disease (DOSD), time to treatment failure and overall survival time (OS) are greater and time to response (TTR) is shorter for subjects receiving second line treatment with panitumumab plus XELOX than for subjects treated with XELOX alone. To assess the differences in overall progression-free and overall survival between subjects with KRAS wild-type and KRAS mutant colorectal cancer who receive XELOX as second-line treatment.

Further Objectives

Exploratory objectives may include investigation of potential correlations between the treatment regimen and EGFR expression, detection of the functional genetic polymorphisms of the EGFR gene, EGFR gene amplification (FISH), EGFR downstream protein and gene expression parameters, proteomics and epigenetics.

Hypothesis

This is a randomized phase II trial which was planned to investigate whether there is evidence that panitumumab in combination with XELOX chemotherapy will safely increase progression-free survival, above that of XELOX alone in subjects with KRAS wild-type metastatic colorectal cancer who have not responded to or progressed after first line therapy with irinotecan and a fluoropyrimidine. Due to its pilot character the nature of the analyses in this study is generally exploratory. However, the prospective sample size determination was planned to ensure reasonable error margins for positive or negative conclusions and decisions drawn from this phase II study.

Study Design

This is a non-comparative randomized, phase II, open-label, three-armed, multicentre trial in which subjects with metastatic colorectal cancer with KRAS-wildtype will be randomized in a 1:1 ratio to receive a 2nd line treatment regimen of panitumumab plus oxaliplatin and capecitabine (XELOX) or XELOX alone. Before randomization tumour of all subjects is analyzed to detect the KRAS mutational status. Subjects were planned to only be randomized into these two arms if the tumour shows KRAS wild-type. Subjects with KRAS mutant colorectal tumours will receive XELOX alone.

Subjects will receive treatment cycles every three weeks. Treatment will continue until subjects are diagnosed with disease progression or intolerable toxicity, at which time the subjects will be withdrawn from the treatment phase. If a subject withdraws from chemotherapy due to toxicity the subjects will be allowed to continue with panitumumab monotherapy with or without one of the chemotherapy components until disease progression. After withdrawing panitumumab and XELOX treatment, all subjects will end the treatment phase and will enter a follow-up phase until 6 months after the last patient stopped treatment (with a safety follow-up visit after 56 days ± 3 days and long term follow-up visits every 12 weeks). During the treatment phase subjects will be evaluated for tumour response every 9 weeks (± one week) through to week 45, and every 12 weeks (± two weeks) thereafter, until disease progression. Subjects with symptoms suggestive of disease progression should be evaluated for tumour response at the time symptoms occur.

To study the effects of human genetic variation on drug responses, additional pharmacogenetic analyses were planned to be conducted. For those subjects that consent to participate in these pharmacogenetic sub-study, DNA was planned to be extracted from blood collected for biomarker assessment and/or tumour samples collected before start of the study.

Response Evaluation

Tumour response assessment will be performed by the investigator according to modified Evaluation Criteria in Solid Tumours (RECIST 1.1) criteria. Subjects will be evaluated for tumour response every 9 weeks through week 45 and every 12 weeks thereafter until disease progression. Responding disease will be confirmed no less than four weeks after the criteria for response are first met. Subjects with symptoms suggestive of disease progression should be evaluated radiographically at the time the symptoms occur. The tumour response should be evaluated with CT/MRI.

Endpoints

Primary Endpoint

Progression-free survival (PFS) rate at 6 months

The primary efficacy analysis will be based on the progression-free survival rate at 6 months, calculated as a “crude” rate by dividing the number of patients alive free from progression at this time point through the total number of randomized patients in the group. For comparison, the rate is also calculated according to the Kaplan-Meier estimation of PFS based on the date of randomisation to date of the first observed disease progression or death (whichever comes first).

Secondary Endpoints (combination or monotherapy)

Objective response rate (ORR)

Incidence of either a confirmed complete or partial response while on study.

Disease control rate (DCR)

Incidence of either a confirmed complete or partial response, or stable disease (SD) while on study.

Duration of response (DOR)

Calculated only for those subjects who have a confirmed complete or partial response, time from first confirmed response to first observed progression or death due to progression (whichever comes first).

Time to response (TTR)

Time from enrolment date to first confirmed complete or partial response.

Progression-free survival (PFS) over the whole study period

Time from enrolment date to date of first observed progression or death (whichever comes first) over the entire trial.

Time to progression (TTP)

Time from enrolment date to date of first observed progression or death due to progression (whichever comes first).

Duration of stable disease (DOSD)

Calculated only for those subjects with a best response of stable disease (SD). Time from enrolment to first observed PD or death due to PD (whichever comes first).

Time to treatment failure

Time from enrollment to the date the decision is made to end the treatment phase for any reason.

Safety endpoints include the incidence and severity of adverse events, changes in clinical safety laboratory parameters, changes in vital signs, compliance with the combination regimen and incidence of dose adjustments.

Overall survival time (OS)

The time from enrolment date to the date of death. Subjects who are known to be alive or for whom a date of death is unknown, will be censored on the later date of the last study assessment or last

known telephone contact.

Further exploratory endpoints (Substudy)

Exploratory endpoints may include investigation of potential correlations between the treatment regimen and EGFR expression, detection of the functional genetic polymorphisms of the EGFR gene, EGFR gene amplification (FISH), EGFR downstream protein and gene expression parameters, proteomics and epigenetics.

Sample Size

The primary analysis was planned to be performed when the last randomized subject with wild-type KRAS tumours has been observed for 6 months. The proportion of subjects in this group, who do not have disease progression after six months of standard treatment with XELOX is expected to be no more than 45%[45)]. Thus, a similar finding in the three-drug combination group would be rated as futile. An improvement by 17% points to 62% (corresponding to an increase in median progression-free survival from 5.2 to 8,7 months and a hazard ratio of 0.6) on panitumumab plus XELOX would be considered very promising and of major clinically relevance. The trial should achieve 80% power for declaring the experimental combination as “promising” when the ***true*** proportion of subjects with progression-free survival at 6-months is 62% or higher, and at the same time keeping the type I error level of erroneously claiming the new combination to be effective (> 62%), although the ***true*** rate is futile (< 45%), below 5%.

52 patients with wild-type KRAS evaluable for progression status at 6 months were required to be observed in the experimental group. The same number was planned to be randomized to the reference arm, leading to a **total sample size of n = 104**. Assuming that 40% of the subjects are not randomized due to mutant KRAS tumours, a total of about 174 subjects was planned to be enrolled.

Summary of Subject Eligibility Criteria

Key inclusion criteria

- Male or female patients aged 18 years or more, with histologically or cytologically-confirmed and radiologically-measurable metastatic colorectal cancer.
- One prior chemotherapy regimen for mCRC consisting of first-line fluoropyrimidine and irinotecan based chemotherapy. Subjects must have disease progression (as assessed by the investigator) and must be no candidates for primary metastectomy.
- Measurable disease according to RECIST 1.1 guidelines. All sites of disease must have been evaluated within 28 days prior to registration / randomization, and diagnosed by the investigator.
- Liver and kidney function within defined ranges and sufficient bone marrow reserve.

Please refer to Section 6 for a complete list of inclusion criteria.

Key exclusion criteria

- Central nervous system metastases, or significant cardiovascular disease.
- Prior anti-EGFR antibody therapy (e.g. cetuximab) or treatment with small molecule EGFR tyrosine kinase inhibitors (e.g. erlotinib).

- Prior treatment with oxaliplatin for metastatic disease. Adjuvant therapy with oxaliplatin based combination for non-metastatic disease is allowed if terminated > 6 months prior to initiation of screening and without progression during the treatment with oxaliplatin.
- Any condition interfering with study drug therapy as defined in the exclusion criteria.

Please refer to Section 6 for a complete list of exclusion criteria.

Investigational Product

Panitumumab is a fully human monoclonal antibody directed against human epidermal growth factor receptor (EGFR), and will be supplied at a concentration of 20 mg/mL in 10 mL vials. The product will be diluted to a total volume of 100 mL pyrogen-free 0.9% sodium chloride (saline) solution, and infused by an infusion pump using an in-line filter (0.2 or 0.22 micron) set up. In the event a subject's actual weight requires a dose higher than 1000 mg, panitumumab will be diluted to a total volume of 150 mL pyrogen-free 0.9% sodium chloride (saline) solution. Final concentration should not exceed 10 mg/mL.

Administration Schedule

Panitumumab at a dose of 9 mg/kg BW every three weeks will be administered on day 1 of each cycle just prior to administration of chemotherapy. Panitumumab will be administered as a 60-minute ± 15 minutes i.v. infusion. In the event a subject's actual weight requires an infusion volume of 150 mL, panitumumab will be administered over 90 minutes ± 15 minutes. The duration of a treatment cycle may be extended, as needed, for the resolution of panitumumab-related toxicities.

Background Chemotherapy

The XELOX regimen is defined as a 2 hour infusion of oxaliplatin 130 mg/m² on day 1 followed by capecitabine 1000 mg/m² bid per os. Capecitabine administration will commence on the evening of day 1 and complete after the morning dose on day 15.

Procedures

Subjects who are eligible for the study and who provided written informed consent will be randomized to receive panitumumab plus XELOX or XELOX alone. Subjects' weight will be measured at the beginning of each cycle and used to calculate the dose to be administered. Radiographic images by computer tomography (CT) or magnetic resonance imaging (MRI) will be performed every 9 weeks ± 1 week through week 45 and every 12 weeks ± 2 weeks thereafter until disease progression, and will be evaluated by the investigator. Clinical evaluations including physical examination will occur prior to each treatment cycle, subjects with symptoms suggestive of disease progression will be evaluated for radiographic progression at the time symptoms occur. A comprehensive haematology and chemistry panel will be collected prior to dosing. Adverse events will be recorded continually through to the safety follow-up visit. Subjects who have signed and dated a pharmacogenomic Informed Consent form will also have an additional 10 ml of whole blood and of 20 ml serum drawn at the beginning of the study prior to panitumumab administration and after that collection of serum again at d1 of each treatment cycle and at the safety follow up and sent to the central lab.

After the treatment phase (disease progression, toxicity, etc.) a termination visit will be performed.

Statistical Considerations

Efficacy

The primary efficacy analysis was planned to be based on the progression-free survival rate at 6 months, calculated as a “crude” rate by dividing the number of patients alive free from progression at this time point through the total number of randomized patients in the group. For comparison, the rate is also calculated according to the Kaplan-Meier estimation of PFS based on the date of randomisation to date of the first observed disease progression or death (whichever comes first). Progression–free survival time, as well as the other secondary time to and duration of event endpoints were planned to be assessed according to Kaplan-Meier and exploratively compared using a log-rank test at a 5% significance level.

Safety

The incidence of adverse events will be summarized with frequency counts and percentages for each study arm.

Actual study course:

Recruitment started in November 2009. Due to a very low recruitment rate the study was closed prematurely in March 2011, with 9 patients only randomized (or allocated to the KRAS mutant arm) up to this time point. As a result, many of the planned procedures described above could not be realized.

Results and conclusions:

Due to the premature closure of the trial with only nine evaluable patients, distributed across the three study arms, no relevant conclusions can be drawn from this trial.

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Appendices

3 ADMINISTRATIVE STRUCTURE AND INVESTIGATORS

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4 INTRODUCTION AND STUDY RATIONALE

4.1 COLORECTAL CANCER

4.1.1 General aspects

Colorectal cancers are rare in developing countries, but are the second most frequent malignancy in Europe and North America. In 2005 CRC is expected to result in 54,290 cancer deaths in the US[29] and over 203,700 in Europe[6]. Of the newly diagnosed patients, 15-25% have metastatic disease at diagnosis[30] and up to 50% of all patients eventually develop metastatic disease[30)38]. If diagnosis is made early and is localized to the bowel mucosa, CRC is generally curable, with 93% five-year survival[45]. However, the 5 year survival rate decreases to 67% upon involvement of adjacent organs and lymph nodes and survival is only 8% in patients with widespread metastatic disease[30)45]. Chemotherapy is the backbone of treatment options in all lines of treatment in CRC regardless of KRAS status. Specifically XELOX chemotherapy has demonstrated that it is both efficacious and has an acceptable toxicity profile as second line treatment of CRC. Pfeiffer et al [44] reported 43% of all patients demonstrated a confirmed response to treatment with this regimen and had not progressed after 6 months when treated with XELOX chemotherapy. Rothenberg et al. [64] showed that XELOX is non-inferior to FOLFOX-4 when administered as second-line treatment in a phase III trial. It is estimated that KRAS Wild-Type patients may demonstrate greater efficacy.

4.1.2 Translational Research

EGFR plays a critical role in tumour progression by stimulating cell cycle progression, invasion, and metastases[34]. The overexpression seen in many tumours maybe due to gene amplification, mutations or transcriptional abnormalities. Currently, immunohistochemistry is the standard method for evaluation of EGFR expression[2)3]. However, there are reports that EGFR expression determined by this method does not correlate with response to blocking agents of the EGFR pathway in lung and colorectal cancers[11)12)53]. The analyses of polymorphisms, the phosphorylation status of EGFR and the expression of downstream targets of EGFR may provide the possibility to identify additional predictive markers in patients treated with Panitumumab.

4.1.3 Treatment of advanced colorectal cancer

For years, effective treatment for CRC was limited to 5-fluorouracil (5-FU). Although it was used traditionally as a single agent, combination with folinic acid has demonstrated a response rate of 23%, with a median survival time of approximately 10 to 12 months[1)].

Two other chemotherapy agents, irinotecan and oxaliplatin, have also been shown to have activity in the treatment of metastatic colorectal cancer (mCRC). Irinotecan, a specific inhibitor of DNA topoisomerase I, demonstrated a significant single-agent activity in the treatment of patients with 5-FU refractory CRC[10)48)]. Furthermore, the addition of irinotecan to 5-FU/LV combination therapy produced a significant improvement over 5-FU/LV alone in response rates, time to progression and in 2 out of this 3 trials also in overall survival in the treatment of patients with previously untreated mCRC[15)51)]. Two other phase 3 trials have also demonstrated superiority when compared to 5FU/LV alone.

Oxaliplatin, a platinum analogue, forms cross-linking adducts and blocks deoxyribonucleic acid replication. Oxaliplatin has been shown to be effective and well-tolerated when administered with bolus and infusional 5-FU (FOLFOX regimen), with neutropenia and sensory neuropathies occurring more frequently than when 5-FU and LV are given alone[13)22)35)]. In first-line advanced colorectal cancer therapy, the FOLFOX4 regimen was shown to be superior to irinotecan, bolus 5-FU, leucovorin (IFL regimen) and to irinotecan and oxaliplatin (IROX regimen), with median overall survival times of 19.5 months, 15.0 months, and 17.4 months, respectively. The response rates and median times to progression were 45%, 8.7 months; 31%, 6.9 months; and 35%, 6.5 months, respectively[21)]. For patients failing irinotecan-based 1st line therapy, the FOLFOX regimen has demonstrated to improve survival when compared to 5FU or oxaliplatin alone[47)].

In conclusion, chemotherapy regimen with 5FU/LV and with oxaliplatin or with irinotecan have become standard of care as chemotherapy backbones in both, 1st and 2nd line therapy. A meta-analysis of phase III trials demonstrated that median overall survival correlates significantly with the percentage of patients receiving all active chemotherapy drugs, 5-FU/FA, oxaliplatin and irinotecan, sequentially[23)]. On the basis of a randomized phase II trial[57)], it has been shown that the efficacy of FOLFIRI followed by FOLFOX6 at progression is similar to the vice-versa-sequence of FOLFOX6 followed by FOLFIRI in terms of progression free and overall survival

(21.5 vs 20.6 months, respectively; p=0.99), allowing patients both options for a sequential treatment.

Oral fluoropyrimidines may prove to be a convenient substitute for infusional 5-FU. Capecitabine is an orally available 5-FU prodrug achieving tumour-selective activation via a triple enzymatic cascade. In the first-line treatment of patients with metastatic CRC capecitabine monotherapy showed comparable efficacy and less toxicity (less neutropenic fever/sepsis, gastrointestinal toxicity and alopecia) compared to bolus 5-FU/leucovorin (Mayo Clinic)[8)9)]. In phase II studies the combination of capecitabine and oxaliplatin showed promising efficacy with manageable toxicity[10)11)12)].

Recently, randomized trials have demonstrated that this combination has a favourable safety profile[2)4)8)37)]. Moreover, data available from the largest 3 trials (ROCHE registration trial, Spanish TTD group and our AIO group) have indicated that progression free survival (as a primary endpoint) of capecitabine combinations is not inferior to 5FU/LV/Oxaliplatin regimens in the 1st line setting[2)8)37)].

Even with the significant improvement in traditional chemotherapy, there remain limitations with this treatment. Therefore, several novel targets are being investigated both as single agents and in combination with chemotherapy to assess the potential for increased efficacy. Some of the most promising targets include the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) and its receptor (VEGFR).

Cetuximab, a chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFR), is licensed by the FDA for use in combination with irinotecan for the treatment of patients with mCRC who have EGFR-expressing tumours that are refractory to irinotecan-based therapy or as monotherapy in irinotecan-intolerant patients who have EGFR-expressing tumours. Within the European Union, the licence permits treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer in combination with chemotherapy or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.in combination with irinotecan for the treatment of patients with mCRC who no longer respond to standard chemotherapy with irinotecan.

Another targeted agent is bevacizumab, which binds and inhibits vascular endothelial growth factor A (VEGF-A), a protein that plays a critical role in tumour

angiogenesis. Bevacizumab is used in combination with intravenous 5-fluorouracil-based chemotherapy and is licensed for first-line treatment of patients with mCRC.

4.2 PANITUMUMAB

(NB: The following paragraphs reflect the information status at the implementation of the study protocol.)

4.2.1 General properties

Panitumumab is a high affinity (Kd = 5 x 10-11 M) fully human IgG2 monoclonal antibody directed against human EGFR. Panitumumab blocks the ligands EGF and TGFα binding to EGFR, inhibits tumour growth, and elicits both tumour regression and eradication of established tumours in murine xenograft tumour models[59)].

4.2.2 Panitumumab clinical experience

Since the commencement of clinical studies 1700 subjects with cancer have been enrolled in panitumumab Phase I, II and III clinical studies, receiving panitumumab doses ranging from 0.01 mg/kg to 5 mg/kg given once every week, 6 mg/kg BW given once every two weeks, and 9 mg/kg BW given once every 3 weeks. Panitumumab has been studied as monotherapy in multiple studies of mCRC and solid tumours (renal, prostate, pancreatic, non small-cell lung, oesophageal and head and neck). Panitumumab has also been studied in combination with chemotherapy for non-small cell lung cancer and with chemotherapy and bevacizumab for mCRC.

4.2.3 Panitumumab clinical safety experience

Dermatological reactions

Dermatologic related reactions, a pharmacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients (approximately 90%) treated with panitumumab, the majority are mild to moderate in nature with approximately 10% severe (grade 3 or higher, NCI-CTC). In clinical studies, subsequent to the development of severe dermatological reactions (including stomatitis), infectious complications including sepsis, in rare cases leading to death, and local abscesses requiring incisions and drainage were reported. Patients who have severe dermatologic reactions or who develop worsening reactions whilst receiving panitumumab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment promptly initiated. It is recommended that patients wear sunscreen and hats and limit sun exposure whilst receiving panitumumab and experiencing rash/dermatological toxicities, as sunlight can exacerbate any skin reactions that may occur. Skin rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities. The median time to first symptom of dermatologic reaction was 10 days, and the median time to resolution after the last dose of panitumumab was 28 days. Paronychial inflammation was associated with swelling of the lateral nail folds of the toes and finger.

Observed adverse effects in the overall mCRC monotherapy set very commonly (≥ 1/10):

rash, erythema, skin exfoliation, pruritus, dry skin, skin fissures, paronychia, diarrhoea, fatigue

commonly (≥ 1/100 to < 1/10): infusion reactions (pyrexia, chills), hypomagnesaemia, hypocalcaemia, hypokalaemia, dehydration, nausea, vomiting, dyspnoea, cough, headache, conjunctivitis, growth of eyelashes, Increased lacrimation, ocular hyperaemia, dry eye, eye pruritus, stomatitis, mucosal inflammation, onycholysis, hypertrichosis, alopecia, nasal dryness, dry mouth and pulmonary embolism.

Acute renal failure has been observed in patients who develop severe diarrhoea or dehydration.

A fatal case of angioedema has been reported in a patient with locally recurrent and metastatic cancer of the tongue who was enrolled in a clinical trial with panitumumab as monotherapy for the treatment of head and neck cancer.

The case of fatal angioedema occurred during the fourth month and after the 4th dose of treatment with panitumumab in a patient aged 71 years with a history of locally recurrent and metastatic squamous cell carcinoma of the tongue. The patient had experienced a prior episode of angioedema approximately 6 days following the 3rd dose of panitumumab. The patient was hospitalized and the angioedema resolved after treatment with steroids and an antihistamine. The administration of an antibiotic (for a calf burn) was originally considered to be the most likely cause of the first event of angioedema. Approximately 2 days after the subsequent exposure to panitumumab (4th dose), symptoms of facial swelling reoccurred. The patient sought medical attention on the following day, at which time she was hospitalized and developed progressive respiratory distress; intubation was declined and the patient died the following morning.

A case of sudden onset of shock during Panitumumab infusion occurred after ¾ of the infusion completed in a 68-year old patient with pharyngeal neoplasm and history of coronary heart disease and triple bypass surgery, who developed a hypersensitivity reaction during an Cetuximab infusion before. Resuscitation attempts were unsuccessful.

Finally one 69 year old patient with metastatic colorectal cancer and a past history of allergic reactions to Oxaliplatin including an anaphylactic reaction requiring admittance to the intensive care unit was treated with Folonic Acid, 5-FU and Panitumumab afterwards. Following completion of the Panitumumab infusion the patient collapsed, was found to be pulseless and apneic. Cardiopulmonary resuscitation was unsuccessful.

Physicians treating patients with panitumumab should consider hypersensitivity reactions, including angioedema, as potentially life-threatening. Depending on the severity and/or persistence of hypersensitivity reactions, panitumumab should be permanently discontinued. In case of severe reactions panitumumab must be discontinued permanently.

KRAS wild-type sub set

The safety profile of panitumumab in patients whose tumour express KRAS wild-type (n = 123)[12] was generally consistent with overall mCRC monotherapy set. The

only differences were that nausea, vomiting, dyspnoea and cough were reported as very common (≥ 1/10) in the KRAS wild-type arm whereas these adverse drug reactions were reported as common (≥ 1/100 to < 1/10) in the overall mCRC monotherapy population.

Pulmonary complications

Patients with a history of, or evidence of, interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies. As Interstitial Lung Disease (ILD) has been observed with EGFR inhibitors, in the event of acute onset or worsening pulmonary symptoms, panitumumab treatment should be interrupted and a prompt investigation of these symptoms should occur. If pneumonitis or lung infiltrates are diagnosed, panitumumab should be discontinued and the patient should be treated appropriately.

Hypomagnesaemia

Patients should be periodically monitored for hypomagnesaemia and accompanying hypocalcaemia every 2 weeks during panitumumab treatment, and 8 weeks after the completion of treatment.

Gastrointestinal disorders

Diarrhoea when reported was mainly mild or moderate in severity. Two percent of patients with KRAS wild-type had diarrhoea reported as severe.

General disorders and administration site conditions

In clinical trials potential infusion reactions (occurring within 24 hours of the first dose) which may include symptoms/signs such as chills, fever, or dyspnoea, were reported in 2% of panitumumab treated patients, of which < 1% were severe (grade 3). No patients had life-threatening (grade 4) or fatal (grade 5) infusion reactions to panitumumab. Most of the symptoms of potential infusion reactions were mild in intensity, resolved without treatment, were isolated occurrences and did not require alteration or interruption of panitumumab administration.

Immunogenicity

Data on the development of anti-panitumumab antibodies has been evaluated using two different immunoassays (an ELISA which detects high-affinity antibodies, and a Biosensor Immunoassay which detects both high and low-affinity antibodies), results from these assays indicated that the overall incidence of a post-dose anti-panitumumab antibody response was low. Pre-dose antibodies were detected in 5 of

636 patients (< 1%) and 16/635 patients (2.5%) tested by the ELISA and Biosensor Immunoassay respectively. Post-dose neutralising antibodies were detected in 1 of 447 patients (0.2%) and 7 of 447 patients (1.6%) tested by the ELISA and Biosensor Immunoassay respectively. Compared with patients who did not develop antibodies, no relationship between the presence of anti-panitumumab antibodies and pharmacokinetics, efficacy and safety has been observed.

Interactions

Patients receiving panitumumab in combination with the IFL regimen [bolus 5-fluorouracil (500 mg/m2), leucovorin (20 mg/m2) and irinotecan (125 mg/m2)] experienced a high incidence of severe diarrhoea, therefore administration of panitumumab in combination with IFL should be avoided.

Shortened progression free survival time and increased deaths were observed when panitumumab was administered in combination with bevacizumab and chemotherapy combinations. A greater frequency of pulmonary embolism, infections (predominantly of dermatologic origin), diarrhoea, and dehydration was also observed in the treatment arms using panitumumab in combination with bevacizumab and chemotherapy. Therefore administration of panitumumab in combination with bevacizumab containing chemotherapy combinations should be avoided.

Pregnancy

There are no adequate data from the use of panitumumab in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Therefore, panitumumab has the potential to cause foetal harm when administered to pregnant women.

Human IgG is known to cross the placental barrier, and panitumumab may therefore be transmitted from the mother to the developing foetus. In women of childbearing potential, appropriate contraceptive measures must be used during treatment with panitumumab, and for 6 months following the last dose. If panitumumab is used during pregnancy or if the patient becomes pregnant while receiving this medicinal product, she should be advised of the potential risk for loss of the pregnancy or potential hazard to the foetus.

Lactation

It is unknown whether panitumumab is excreted in human breast milk. Because human IgG is secreted into human milk, panitumumab might also be secreted. The potential for absorption and harm to the infant after ingestion is unknown. It is recommended that women do not breast feed during treatment with panitumumab and for 3 months after the last dose.

Fertility

Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys. Panitumumab may impact the ability of a woman to become pregnant.

4.2.4 Panitumumab clinical efficacy experience

Panitumumab is being studied as a monotherapy and in combination with chemotherapy in several clinical studies. Efficacy has been observed in various tumour types when given as both monotherapy and in combination with chemotherapy.

Seven hundred and twenty three subjects with metastatic colorectal cancer treated previously with at least two prior lines of chemotherapy were administered panitumumab monotherapy in one of four Phase II or III clinical trials. The response rate ranged from 8-13% with a disease control rate of 28-44%. The median time to response ranged from 8-11 weeks and the duration of response was 13-18 weeks. The median time of progression-free survival was 8-14 weeks. In the multi-centre, open-label, controlled phase 3 study conducted in Europe, Australia and Canada, 463 mCRC patients who had failed standard chemotherapy, including oxaliplatin and irinotecan were randomized to receive panitumumab plus best supportive care (n=231) or best supportive care alone (n=232). Patients who received panitumumab 6 mg/kg every two weeks showed a 46 % decrease in tumour progression rate (primary endpoint) versus those who received best supportive care alone ($p < 0.0001$).

In clinical studies with panitumumab as monotherapy, mild to moderate diarrhoea has been reported. Hypomagnesaemia has also been reported, with the majority of events Grade 1 or 2 in severity. Other non-dermatological manifestations reported during monotherapy studies include asthenia, pain, constipation, nausea, fever,

back pain, abdominal pain, anorexia, diarrhoea, arthralgia, dizziness, increased cough, dyspnoea, vomiting, and upper respiratory infection.

Based on an analysis of all patients receiving panitumumab monotherapy (N = 920), the most commonly reported adverse reactions are skin reactions occurring in approximately 90% of patients. These reactions are related to the pharmacologic effects of panitumumab, and the majority are mild to moderate in nature with approximately 10% severe (grade 3 or higher, NCI-CTC). The most frequently-reported serious, treatment-related adverse event was hypomagnesaemia, reported in seven subjects (1%). All other treatment-related serious adverse events were reported in <1% of subjects.

Panitumumab Combination Therapy Studies Panitumumab is currently being studied in combination with chemotherapy in subjects with CRC and non small-cell lung cancer. In these studies, skin-toxicities were reported to be similar in nature and severity to those reported in the monotherapy studies.

In the CRC studies involving administration of panitumumab in combination with IFL, diarrhoea was more frequently reported than when compared to the monotherapy studies. Other frequent adverse events when panitumumab was used in combination with IFL were skin toxicity, asthenia and nausea.

In a Phase II non small-cell lung cancer study in which panitumumab was administered in combination with paclitaxel and carboplatin, approximately 80% of subjects have been reported to have a dose-related, reversible, acneiform, or maculopapular skin rash similar to that seen in the monotherapy studies. Reported less frequently were fingertip or nail bed infection and inflammation. Beyond these skin effects, the most frequent AEs reported as related to panitumumab were asthenia, diarrhoea, nausea, and throat irritation. Examining AEs overall, regardless of relationship, the most frequently reported AEs other than skin rash were nausea, asthenia, alopecia, myalgia, arthralgia, constipation, diarrhoea, vomiting, and throat irritation.

Panitumumab therapy was studied in a clinical trial which included more than 400 subjects receiving panitumumab in combination with bevacizumab and either oxaliplatin or irinotecan-based chemotherapy [65)]. A recent unplanned interim survival analysis of the data in this study showed that subjects who did not receive panitumumab had better survival (lived longer). Some subjects who received panitumumab experienced more severe adverse effects than those who did not get

panitumumab. These effects included diarrhoea (leading to severe dehydration), dehydration, severe infections and the presence of clots in the lung (pulmonary embolism) that in some cases were fatal.

4.2.5 Panitumumab pharmacokinetic studies

Early Pharmacokinetic Studies showed, that the Panitumumab concentration increases non-linearly with dose, most likely due to progressive saturation of a fixed EGFR sink [66].

At a 2.5 mg/kg dose, panitumumab clearance was close to the typical clearance range of human IgG antibodies that are not subject to an antigen sink, but are cleared via the reticuloendothelial system. This observation supports the hypothesis that the majority of the EGFR sink was saturated at the 2.5 mg/kg weekly dose [66].

Panitumumab is administered at 6 mg/kg once every 2 weeks [67]. The elimination half-life of panitumumab under steady-state conditions was approximately 7.5 days (range: 3.6 to 10.9 days); elsewhere, the half-life when non-linear clearance is fully saturated was reported to be 15.9±1.57 days (95% CI, 12.7-19.1) [66].

Weiner et al shows, that the observed concentration-time course for 6 mg/kg every 2 weeks and 9 mg/kg every 3 weeks panitumumab compared with the observed and fitted concentration-time course for 2.5 mg/kg weekly [68].

The minimal serum panitumumab concentrations (C_{trough}) were similar among the 2.5 mg/kg weekly, 6.0 mg/kg every 2 weeks and 9.0 mg/kg every 3 weeks doses, with steady-state reached after about 6 weeks for all schedules.

The observed steady-state level of 50 mcg/mL for the 2.5 mg/kg weekly dose accurately predicted that this level would be reached by 6.0 mg/kg every 2 weeks and 9.0 mg/kg every 3 weeks dosages [68].

4.3 STUDY RATIONALE AND HYPOTHESIS, RISK-BENEFIT ASSESSMENT

XELOX chemotherapy is rapidly becoming the regimen of choice for initial treatment of mCRC patients at many institutions throughout Europe. The use of an oral

formulation of 5-FU (capecitabine) instead of standard i.v. 5-FU is increasingly accepted in clinical practice in both, 1st and 2nd line treatment. Furthermore data are emerging that CRC patients may not benefit from EGFR-Inhibition if the tumour possess a KRAS mutation.

This study has been designed to investigate whether adding panitumumab to XELOX increases the efficacy of this regimen in the second-line treatment of KRAS wild-type mCRC. Furthermore this study was to evaluate the prognostic impact between KRAS wild-type and KRAS mutant mCRC which were treated with XELOX alone. Chemotherapy is the backbone of treatment options in all lines of treatment in CRC regardless of KRAS status. Specifically XELOX chemotherapy has demonstrated that it is both efficacious and has an acceptable toxicity profile as second line treatment of CRC. Pfeiffer et al [44)] reported 43% of all patients demonstrated a confirmed response to treatment with this regimen and had not progressed after 6 months when treated with XELOX chemotherapy. It is estimated that KRAS Wild-Type patients may demonstrate greater efficacy.

In order to enhance the therapeutic outcome of patients with metastatic colorectal cancer, development of new combination treatment regimens and schedules is essential. Aside from limited cases of resectable metastatic disease, metastatic colorectal cancer cannot be cured with the currently available chemotherapy regimens, and there is a continued need to improve the current treatment. Epidermal growth factor receptor has been shown to play an important role in carcinogenesis, and inhibiting EGFR with anti-EGFR antibody has been shown to have clinical efficacy in the treatment of metastatic colorectal cancer[52)].

This is a randomized phase II study. The hypothesis is that the addition of panitumumab to chemotherapy (XELOX) will safely further increase progression-free survival than XELOX chemotherapy alone as 2nd line treatment of KRAS wild-type metastatic colorectal cancer. Due to its pilot character (and actually its premature termination with a very low patient number recruited) the nature of the analysis in this study is generally explorative. However, the prospective sample size determination was planned to ensure reasonable error margins for the positive or negative conclusions and decisions to be drawn from this phase II study.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

To assess the differences in progression-free survival at 6 months in subjects with KRAS wild-type metastatic colorectal cancer receiving second line treatment (after failure of a previous irinotecan and 5FU based regimen) with panitumumab plus XELOX compared to the treatment with XELOX alone, without major safety problems.

5.2 SECONDARY OBJECTIVES

To assess that, for subjects with KRAS wild-type metastatic colorectal cancer, objective response rate (ORR), disease control rate (DCR), duration of response (DOR), time to progression (TTP), duration of stable disease (DOSD), time to treatment failure and overall survival time (OS) are greater and time to response (TTR) is shorter for subjects receiving second line treatment with panitumumab plus XELOX than for subjects treated with XELOX alone. To assess the differences in overall progression-free and overall survival between subjects with KRAS wild-type and KRAS mutant colorectal cancer which receive XELOX as second-line treatment.

5.3 EXPLORATORY OBJECTIVES

Exploratory objectives may include investigation into potential correlations between the treatment regimen and EGFR expression, detection of the functional genetic polymorphisms of the EGFR gene, EGFR gene amplification (FISH), EGFR downstream protein and gene expression parameters, proteomics and epigenetics.

6 INVESTIGATIONAL PLAN

6.1 GENERAL ASPECTS

6.1.1 Study design

This is a non-comparative randomized, phase II, open-label, three-armed, multicentre trial in which subjects with metastatic colorectal cancer with KRAS wildtype were to be randomized in a 1:1 ratio to receive a 2nd line treatment regimen of panitumumab plus oxaliplatin and capecitabine (XELOX) or XELOX alone, if the tumour shows a KRAS wild-type. The protocol required the following planned procedures: Before randomization tumor of all subjects will be analyzed to detect the KRAS status. Subjects will only be randomized into these two arms if the tumour shows KRAS wild-type. Subjects with KRAS mutant colorectal tumours will receive XELOX alone. KRAS status may be determined in a local laboratory. Additionally all samples will be sent to central laboratory in order to have distinct comparative results.

Subjects with evidence of complete response, partial response or stable disease will receive panitumumab and/or chemotherapy until disease progression, unacceptable toxicities or withdrawal of consent. Patients with stabilisation of tumour volume who are not appropriate for ongoing chemotherapy may continue on panitumumab alone. Subjects with evidence of disease progression will be discontinued from treatment and will be followed up until 6 months after the last patient stopped treatment (including a safety follow-up of 56 days).

Tumour response assessment will be performed by the investigator per RECIST 1.1 criteria[55)]. Subjects will be evaluated for tumour response every 9 weeks ± 1 week through week 45 and every 12 weeks ± 2 weeks thereafter until radiographic disease progression. Responding disease will be confirmed no less than four weeks after the criteria for response are first met. Subjects with symptoms suggestive of disease progression should be evaluated radiographically at the time the symptoms occur. The tumour response should be evaluated with CT / MRI.

The analyses of polymorphisms, the phosphorylation status of EGFR and the expression of the downstream targets of EGFR was planned to be also analysed in order to provide the possible identification of additional predictive markers in patients treated with Panitumumab. For these pharmacogenetic analyses DNA will

be extracted from the blood collected for biomarker assessment and/or tumour samples collected before the study. The additional analyses required a specific subject's informed consent.

6.1.2 Number of centres

Approximately 25 sites in Germany were planned to participate.

6.1.3 Estimated and actual study duration

Recruitment phase: 24 months

Duration of treatment: approximately 6 months

Follow-up phase: 6 months after the last patient stopped treatment (incl. 56 days safety follow-up)

Estimated end of the study: October 2012

Actual study course:
Recruitment started in November 2009. Due to a very low recruitment rate the study was closed prematurely in March 2011, with 9 patients only randomized (or allocated to the KRAS mutant arm) up to this time point.

6.1.4 Study duration for participants

The protocol provided the following planned procedures: Subjects eligible for participation in the study will sign an informed consent and patients with KRAS-wildtyp will be randomized into one of the two treatment arms. Subjects with KRAS mutant colorectal tumours will receive XELOX alone. KRAS status may be determined in a local laboratory. Additionally all samples will be sent to central laboratory in order to have distinct comparative results Subjects will receive study treatment until disease progression or unacceptable toxicity. It is expected that subjects will be on treatment approximately 6 months. Subjects will enter a follow-up

phase. The follow-up will be ongoing until 6 months after the last patient stopped treatment. The follow-up phase includes a 56 ± 3 days safety follow-up.

Due to the premature stop of the trial, follow-uo was abridged in individual patients.

6.1.5 Treatment after the end of treatment in the study

After the end of the treatment in the study the subjects are treated according to the knowledge then available. Panitumumab will not be provided to subjects outside the study or after the end of treatment in the study.

6.2 PATIENT SELECTION

6.2.1 Inclusion Criteria

1) Competent to comprehend, sign, and date an IEC-approved informed consent form, written informed consent.

2) Of either gender and aged 18 years or more.

3) Diagnosed with histologically or cytologically confirmed and inoperable relapsed/refractory metastatic adenocarcinoma of the colon or rectum.

4) One prior chemotherapy regimen for mCRC consisting of first-line fluoropyrimidine and irinotecan based chemotherapy. Subjects must have disease progression (as assessed by the investigator) and must be no candidates for primary metastectomy.

5) Measurable disease according to RECIST 1.1 guidelines. All sites of disease must have been evaluated 28 days prior to registration / randomization, and diagnosed by the investigator.

6) Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

7) Available tumour tissue and known KRAS mutation status.

8) Haematologic function, as follows (within 7 days prior to registration/randomization)

Absolute neutrophil count (ANC) > 1500/mm^3

Platelet count ≥ 100,000/mm^3

Hemoglobin ≥ 9 g/dl (5,8 mmol/l)

9) Renal function, as follows (within 7 days prior to registration/randomization)

Creatinine < 1,36 mg/dl (120 µmol/l)

Creatinine clearance > 50ml/minute as estimated from serum creatinine concentration according to the method of Cockroft and Gault

10) Hepatic function, as follows (within 7 days first prior to registration/ randomization)

Aspartate aminotransferase (AST) ≤ 2.5 x ULN (if liver metastases ≤ 5 x ULN)

Alanine aminotransferase (ALT) ≤ 2.5 x ULN (if liver metastases ≤ 5 x ULN)

Bilirubin ≤ 1.5 x ULN

11) Metabolic function, as follows (within 7 days prior to registration/randomization)

Magnesium ≥ lower limit of normal

Calcium ≥ lower limit of normal

6.2.2 Exclusion Criteria

1) Central nervous system (CNS) metastases. Exceptions that are eligible include subjects who have been treated, have asymptomatic central nervous system metastases, and have been off steroids at least 30 days before initiating study treatment.

2) Other malignant tumours less than five years old. Exceptions include basocellular carcinoma, *in situ* cancer of the cervix of the uterus, or any curatively treated other malignancies without evidence of disease for more than five years.

3) Significant ascites or pleural effusion.

4) Prior anti-EGFR antibody therapy (e.g. cetuximab) or treatment with small molecule EGFR tyrosine kinase inhibitors (e.g. erlotinib).

5) Prior treatment with oxaliplatin for metastatic disease. Adjuvant therapy with oxaliplatin based combination for non-metastasised disease is allowed if terminated > 6 months prior to initiation of screening and without progression.

6) Concomitant therapy with sorivudine or analogue compounds.

7) Known previous or ongoing abuse of narcotic drug, other medication or alcohol.

8) Prior radiation of indicator lesion(s), except for documented progression during radiation and termination of radiotherapy at least four weeks before initiating study treatment.

9) Lack of physical integrity of the upper gastrointestinal tract or malabsorption

10) Significant cardiovascular disease including New York Heart Association (NYHA) grade II or greater congestive heart failure, peripheral arterial occlusive disease stage II or greater, symptomatic coronary heart disease, insufficiently treated arterial hypertension, unstable angina or myocardial infarction within 12 months before initiating study treatment or a history of ventricular arrhythmia.

11) History or evidence upon physical examination of CNS disease unless adequately treated (e.g. primary brain tumour, seizure not controlled with standard medical therapy, brain metastases or history of stroke).

12) History of interstitial pneumonitis or pulmonary fibrosis or evidence of interstitial pneumonitis or pulmonary fibrosis on baseline chest CT scan.

13) Pre-existing polyneuropathy grade ≥ 1 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), except for loss of tendon reflex as the only symptom.

14) Treatment for systemic infection within 14 days before initiating study treatment.

15) Active inflammatory bowel disease, serious gastric ulceration or other bowel disease causing chronic diarrhoea (defined as > 4 loose stools per day).

16) History of Gilbert's syndrome.

17) Known Dihydropyrimidine deficiency or dihydropyrimidine dehydrogenase (DPD) deficiency.

18) Thrombosis or severe bleeding within six months prior to entry into the study (except for bleeding of the tumour before its surgical resection), evidence of bleeding diathesis or coagulopathy, or current or recent (within 10 days prior to initiation of study treatment) use of full-dose oral or parenteral anticoagulants for therapeutic purposes.

19) Proteinurea > 1+ according to dipstick urinalysis, or urinary excretion of protein > 1 g/24 hours within seven days prior to initiation of study treatment.

20) History of any medical condition that may increase the risks associated with study participation or may interfere with the interpretation of the study results.

21) Known positive test for human immunodeficiency virus infection, hepatitis C virus or chronic active hepatitis B infection.

22) Known allergy to the investigational product, to any of its excipients, to monoclonal antibodies, or to any of the components of the chemotherapy regimen.

23) Any co-morbid disease that would increase risk of toxicity.

24) Any kind of disorder that compromises the ability of the subject to give written informed consent and/or comply with the study procedures.

25) Any investigational agent within 30 days or five half lives of that investigational agent before initiation of study treatment or participation in another clinical trial.

26) Must not have had a major surgical procedure within 28 days of initiation of treatment.

27) Subject who is pregnant or breast feeding.

28) Woman or man of childbearing potential not consenting to use adequate contraceptive precautions (intrauterine contraceptive device, contraceptive implants, injectables (hormonal depot), transdermal hormonal contraception (contraceptive patch), sexual abstinence or vasectomised partner) during the course of the study and for six months after the last study drug administration.

29) Subject unwilling or unable to comply with study requirements.

6.3 SUBJECT ENROLMENT

The protocol describes the following planned procedures: Prior to randomization the KRAS mutation status should be determined by a laboratory (local or central). Additionally the KRAS status for all participants in this study will be determined centrally in the central laboratory in Dresden. Therefore the tumour block (alternatively a minimum of ten and ideally 20 unstained slides) will be sent to the central laboratory upon start of screening. Upon notification that a patient entered the screening phase of the study a fax will be send to central laboratory (see Appendix K). This is to ensure a tracking of the tumour tissue by the central laboratory. Upon shipment of the tumour material a corresponding paper sheet must be sent together with the tissue (see Appendix K). If the KRAS status is evaluated by the central laboratory, the investigator has to be informed about the KRAS status by the central laboratory.

A subject is considered enrolled when he or she has been registered and assigned to study treatment allocation.

For registration/randomization at

iOMEDICO AG

Fax: 0761-15242-10

the following data were needed:

- name / number of the centre
- name of the investigator
- date of informed consent
- assurance that all inclusion criteria and none of the exclusion criteria are fulfilled
- ECOG performance status (0/1 or 2)
- prior treatment with bevacizumab (yes or no)
- KRAS-status

Upon confirmation of eligibility and confirmation of KRAS wild-type status, study subjects were randomized to treatment arm 1 and 2 in 1:1 ratio and iOMEDICO allocated the randomization number from the study specific computer-generated

randomization list. Study subjects with KRAS mutant mCRC were registered and assigned to XELOX alone (Arm 3):

Arm 1: Panitumumab plus XELOX (KRAS wild-type)

Arm 2: XELOX alone (KRAS wild-type)

Arm 3: XELOX alone (KRAS-mutant)

The subject's randomization / registration number, study group/allocated study medication and registration / randomization date were entered on the form which is then faxed back to the clinical site.

Following registration / randomization, study treatment should commence within seven days.

6.4 STUDY TREATMENT PROCEDURES AND ASSESSMENTS

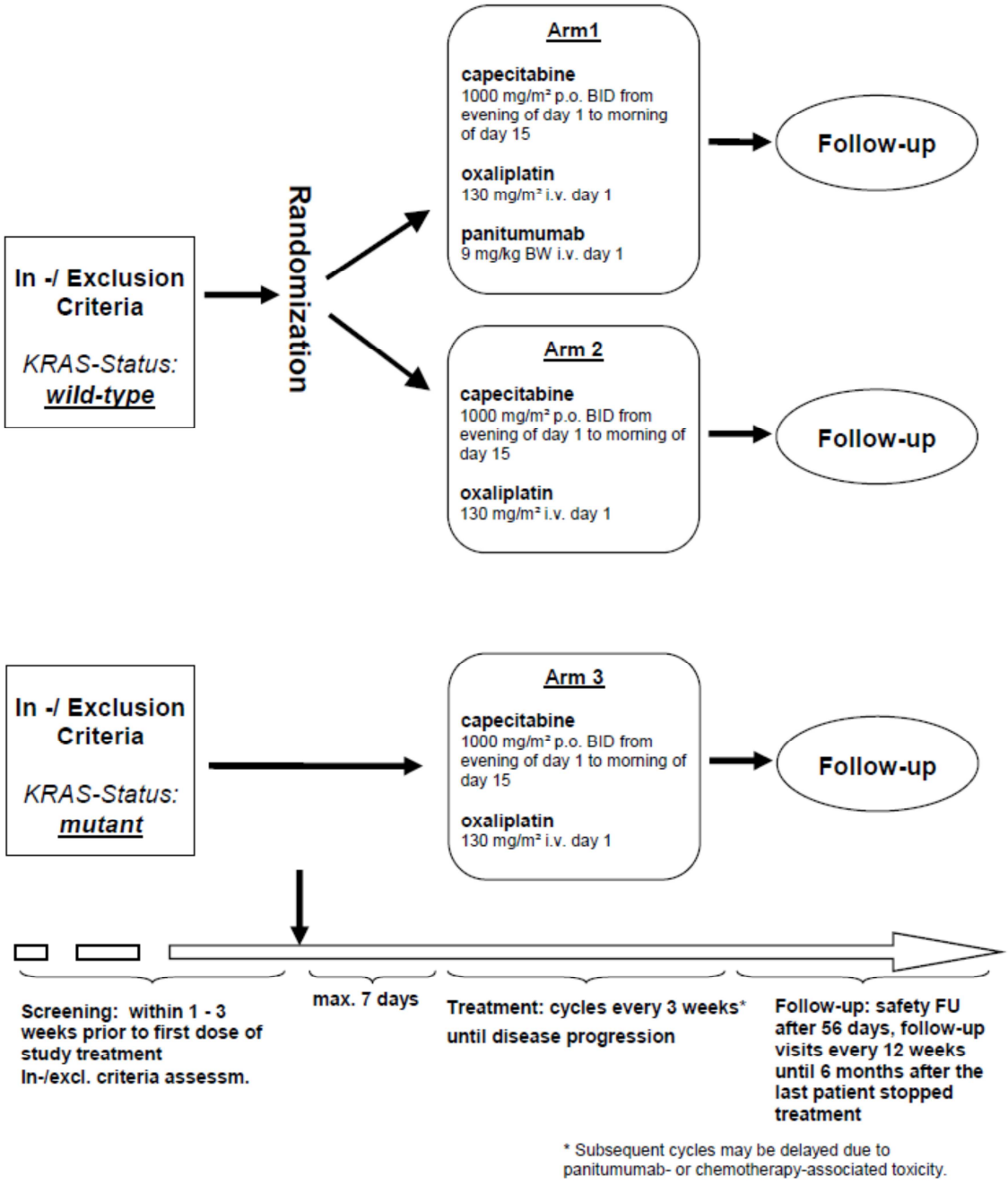
The general outline of the study is shown in the overview on the next page. Further details on

- therapy dosages, administration and schedules
- treatment modifications
- discontinuation of treatment
- concomitant therapy
- surgery

are provided in section 6 of the study protocol (appendix 1).

Additional information on all study assessments and evaluation procedures is to be found in section 7 of the study protocol (appendix 1), and in section 9 of the study protocol for safety aspects, respectively. Planned procedures on withdrawal and replacement of subjects are described in section 8 of the study protocol (appendix 1).

Overview of study design and treatment plan



6.5 PROTOCOL AMENDMENT

The study protocol had been amended once, with the final version **(FINAL 4, 11.01.2010,** cf. appendix 1) replacing version **FINAL 3, 22.07.2009**. Cf. appendix 2 for details on the amendment.

7 STATISTICAL CONSIDERATIONS AND STUDY ENDPOINTS

7.1 INTRODUCTION AND PRIMARY ENDPOINT DEFINITION

This is a randomized, phase II, open label, multi-centre parallel group study with two treatment groups, designed to test the clinical hypothesis that treatment with the combination of panitumumab plus XELOX shows evidence for an improved progression-free survival (PFS) in subjects with metastatic colorectal cancer and KRAS wild-type tumours that have failed to respond to first line treatment than treatment with XELOX alone.

The estimation of the PFS rate of the panitumumab combination is to be based on an explorative pilot study, since immediate embarking on a large scale comparative efficacy trial would not be acceptable from the point of view of resources. Moreover, this would induce ethical objections, as it does not seem to be justifiable to expose a large number of patients to an experimental approach without any exploratory indications of an improved risk-benefit ratio.

In this situation, a randomized phase II trial with a standard treatment control group proves to be an appropriate research design in order to achieve a valid efficacy estimation. This type of cancer study design is propagated since the early 1980s, especially by representatives of the National Cancer Institute (Leventhal et al., 1988; Buyse, 2000) [61),62)]. The key idea of randomizing already in the phase II of the treatment development offers the opportunity to reduce some of the result variability which is typically encountered in phase II trials, especially caused by patient selection phenomena and investigator bias. Thus, with a randomized control group at hand, differences obtained for the two treatments will more likely represent real differences in efficacy rather than differences in patient selection, clinical evaluation, and other factors, since these factors will be handled in similar fashion for both arms of the study. The purpose of randomized phase II designs is not a formal, rigorous comparison of two or more treatment arms, but rather a reduction in certain sources of variability that afflict conventional phase II trials and their comparison across studies. Subjects are randomized to XELOX plus panitumumab or XELOX alone in the ratio of 1:1. The randomisation is stratified according to pre-treatment with bevacizumab or no such pre-treatment and baseline ECOG performance status (0/1 vs. 2).

The **primary efficacy analysis** is based on the progression-free survival rate at 6 months, calculated as a "crude" rate by dividing the number of patients alive free from progression at this time point through the total number of randomized patients in the group. For comparison, the rate is also calculated according to the Kaplan-Meier estimation of PFS based on the date of randomisation to date of the first observed disease progression or death (whichever comes first). Subjects who have not progressed while on study and have not died while on study are censored at the last evaluable disease assessment date. This analysis, and the analysis of all other efficacy endpoints, are based on the All Enrolled Analysis subset.

Tumour response assessment are performed by the investigator according to the RECIST 1.1 criteria[55]. Subjects are evaluated for tumour response every 9 weeks through week 45 and every 3 months thereafter until radiographic disease progression. Subjects with symptoms suggestive of disease progression should be evaluated radiographically at the time the symptoms occur.

7.2 ADDITIONAL STUDY ENDPOINTS, SUBSETS, AND COVARIATES

7.2.1 Secondary endpoints (combination or monotherapy)

Progression-free survival time over the entire trial (PFS) for subjects with KRAS wild-type tumours

The time from randomization to date of first observed progression or death from any cause (whichever comes first) for KRAS wildtype subjects randomized to receive XELOX ± panitumumab. Subjects who have not progressed while on study and have not died while on study are censored at the last evaluable radiographic assessment date.

Progression-free survival time over the entire trial (PFS) for subjects receiving XELOX only (KRAS wild-type and KRAS mutant status)

The time from randomisation to date of first observed progression or death from any cause (whichever comes first) for subjects that received XELOX only (Arm 2 and 3). Subjects who have not progressed while on study and have not died while on study are censored at the last evaluable radiographic assessment date.

Objective response rate (ORR) over the entire treatment period

Incidence of either a confirmed complete or partial response while on treatment (combination, or monotherapy if chemotherapy is withdrawn); subjects prematurely discontinuing without a post-baseline tumour response assessment or subjects with an observed complete or partial response that is not confirmed are considered non-responders.

Disease control rate (DCR)

Incidence of either a confirmed complete or partial response, or stable disease (SD) while on treatment; subjects prematurely discontinuing without a post-baseline tumour response assessment or subjects with an observed complete or partial response that is not confirmed are considered non-responders otherwise.

Duration of response (DOR)

Calculated only for those subjects who have a confirmed complete or partial response, time from first confirmed response to first observed progression or death due to progression (whichever comes first). For subjects who respond and have not progressed while on study or died for reasons other than progression while on study, duration of response are censored at their last evaluable radiographic disease assessment date.

Time to response (TTR)

Time from enrolment date to first confirmed complete or partial response; subjects with a best response of stable disease at their last evaluable assessment date are censored at this date and subjects with best response progressive disease while on study are censored after the last response is observed for all subjects.

Time to progression (TTP)

Time from registration / randomization to date of first observed progression or death due to progression (whichever comes first). For subjects who have not progressed while on study or died for reasons other than progression while on study, time to progressive disease are censored at their last evaluable radiographic disease assessment date.

Duration of stable disease (DoSD)

Calculated only for subjects with a best response of stable disease. Time from registration / randomization to first observed PD or death due to PD (whichever comes first). For subjects who have not progressed while on study or died for reasons other than PD while on study, duration of SD are censored at their last evaluable assessment date.

Time to treatment failure

Time from registration / randomization to the date the decision was made to end the treatment phase for any reason. For subjects who remain in the treatment phase at the time of the analysis, time to treatment failure are censored at the date of their last on-study assessment.

Overall survival time (OS)

The time from registration / randomization date to the date of death. Subjects who are known to be alive or for whom a date of death is unknown, are censored on the later date of the last study assessment or last known telephone contact.

7.2.2 Analysis subsets

The primary analysis of efficacy endpoints is performed on the All Enrolled Subjects Analysis Set defined as all subjects who have provided informed consent, who have enrolled and who have been allocated to a treatment group.

Sensitivity analyses of efficacy endpoints is performed on the Per Protocol Analysis Set defined as the subset of the all available subjects analysis set who have received at least 80% combination therapy during the treatment period and who have no major protocol deviations thought to impact on the efficacy conclusions of the trial.

Safety analyses are performed using the All Treated analysis set, defined as subjects in the all enrolled subjects analysis set who have received at least one dose of any constituent of XELOX or panitumumab.

7.2.3 Covariates

The efficacy profile may be explored within subgroups defined by the following covariates:

- Potential biomarkers
- ECOG performance status
- Primary site of disease (colon and rectum)
- Number of metastatic disease sites (number of affected organs)
- Prior treatment with bevacizumab
- Age
- Sex
- KRAS Status

7.3 SAMPLE SIZE CONSIDERATIONS

It is expected that about 40% of the tumours of the subjects are KRAS mutated. The proportion of subjects in this group, who do not have disease progression after six months of standard treatment with XELOX is expected to be no more than 45%. Thus, a similar finding in the three-drug combination group would be rated as futile. An improvement by 17% points to 62% (corresponding to an increase in median progression-free survival from 5.2 to 8,7 months and a hazard ratio of 0.6) on panitumumab plus XELOX would be considered very promising and of major clinically relevance. The study was expected to recruit all the required subjects in no more than 24 months. Each subject was planned to be followed up for at least 6 months and no loss to evaluability is expected, due to the intent-to-treat basis of the primary analysis. The trial should achieve 80% power for declaring the experimental combination as “promising” when the ***true*** proportion of subjects with progression-free survival at 6-months is 62% or higher, and at the same time keeping the type I error level of erroneously claiming the new combination to be effective (> 62%), although the ***true*** rate is futile (< 45%), below 5%.

According to the design approach by Fleming (1982) [63)], 52 patients with wild-type KRAS evaluable for progression status at 6 months are required to be observed in the experimental group. The same number of subjects was planned to be

randomized to the reference arm, leading to a **total sample size of n = 104**.. Assuming that 40% of the subjects are not randomized due to mutant KRAS tumours, a total of about 174 subjects was planned to be enrolled. The primary analysis was planned to be performed when all patients with wild-type KRAS tumours have been observed for 6 months.

7.4 ACCESS TO INDIVIDUAL SUBJECT TREATMENT ASSIGNMENTS

This is an open label study. Information about treatment assignments are freely available.

7.5 PLANNED INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

Interim analyses for presentation purposes might have been required. Safety data might have been summarised along with secondary efficacy endpoints depending on the rate of enrolment and information that is available. The primary endpoint (PFS rate) was not allowed to be analysed as part of an interim analysis.

7.6 PLANNED METHODS OF ANALYSIS

7.6.1 General approach/considerations

The protocol describes the following planned procedures: Efficacy analyses will be based on radiographic images collected during the study. An objective response will only be considered an objective response if it is confirmed by a scan no less than four weeks after the criteria for response are first met. Any scan that is rated UE (unevaluable) by the investigator will be omitted from the analysis (considered as if there was no scan).

For continuous endpoints, the mean with standard deviation (if appropriate), median, 25^{th} percentile, 75^{th} percentile, minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided. Confidence interval will be calculated for parameters of major importance. For time to event data, the standard Kaplan-Meier method will be used to provide survival curves,

point estimates and 95% central confidence intervals for the median. Additionally, the time to and duration of event endpoints may be calculated within subgroups defined by the covariates defined in Section 10.1.3 and Cox proportional hazards modelling will be used to explore these relationships.

7.6.2 Analysis of study endpoints

Primary endpoint

The definition of the primary endpoint is described in section 7.1. In addition to the confidence intervals determined for each study group, confidence intervals will also be provided for the rate difference and odds ratio. A sensitivity analysis will be performed using the Per Protocol analysis set (excluding patients with less than 80% of protocol therapy given or having a major protocol violation, either before detection of progression or within the 6 month period from randomisation, respectively) to assess the robustness of conclusions.

Time to and duration of event endpoints

Progression–free survival time, as well as the other secondary time to and duration of event endpoints will be assessed according to Kaplan-Meier and exploratively compared using a log-rank test at a 5% significance level on the All Enrolled analysis set.

The time to and duration of event endpoints may additionally be calculated within subgroups defined by the covariates given in Section 10.1.3. and Cox proportional hazards modelling will be used to explore these relationships.

Objective response rate and disease control rate

The objective response rate and disease control rate over the entire study (“best response”) will be reported using two-sided 95% confidence intervals for the All Enrolled Subjects analysis set.

The response rate and disease control rate, with associated 95% confidence intervals, may be estimated within the subgroups defined by the list of covariates defined in section 10.1.3. Logistic regression techniques may be used to explore the relationship between response, biological marker status and other covariates.

Safety

All safety data will be reported overall and may be reported by the list of covariates defined in section 10.1.3. Safety presentations will be based on the All Treated analysis set.

Subject incidence rates of adverse events (including all, serious, fatal, grade 3, grade 4, and treatment related) will be tabulated using the NCI CTCAE v3.0 with the exception of skin toxicity, per section 6.2.

Tables and/or narratives of deaths through the post-treatment safety follow-up, and treatment-related SAEs will be provided.

7.7 STATISTICAL ANALYSIS PLANS / ANALYSES ACTUALLY PERFORMED

Based on the originally planned procedures outlined above, a statistical analysis plan (V. 1.0, dated from 14-01-10, cf. appendix 6) was written. After the decision on early closure of the trial, an abridged version was implemented (V. 2.0, dated from 01-06-11, cf. appendix 7), on which the analyses in section 9 to 13 of this report are based.

8 REGULATORY, ETHICAL AND OTHER ADMINISTRATIVE ISSUES

The regulatory, ethical, confidentiality and GCP standards as well as procedures for amendments, documentation, reports, publication and financing of this trial are described in section 12 of the study protocol (appendix 1).

The initial positive vote on the protocol and the participating institutions from the "Ethikkommission der Landesärztekammer Hessen", Frankfurt/Main, Germany, was obtained on 22-07-2009 (appendix 3). The amendment (appendix 2) was approved by the same committee on 12-04-2010 (appendix 3).

Federal authority approval was obtained from the Paul-Ehrlich-Institut, Langen, Germany, on 28-07-2009 (primary protocol version) and 01-04-2010 (amendment).

9 STUDY PATIENTS

9.1 RECRUITMENT

A total of 10 patients were recruited into the study between November 2009 and the premature study closure in March 2011, as shown in Tab. 1.

Tab. 1 Course of recruitment

Year quarter	Number of patients (n=10)
IV/2009	1
I/2010	1
II/2010	2
III/2010	1
IV/2010	4
I/2011	1*

* Patient no. 13 was recruited shortly before trial closure, and not randomized any more.

The recruitment of the patients by participating centre/investigator is presented in Tab. 2.

Tab. 2 Recruitment by centre

Center no.	Centre/investigator	Number of patients (n=10)
1	Grunewald, Frankfurt	2
3	Depenbusch, Gütersloh	1
5	Eschenburg, Güstrow	1
6	Fischer von Weikersthal, Amberg	1
20	Ladda, Neumarkt	1
21	Jacobasch, Dresden	1*
26	Kirchen, Trier	1
27	Egger, Lahr	1
28	Hennemann, Duisburg	1

* Patient no. 13 was recruited shortly before trial closure, and not randomized any more.

9.2 DATA AND EVALUABILITY STATUS, ANALYSIS POPULATIONS

An overview of the study population and its inclusion in the various statistical analyses is given in Tab. 3. Patient no. 13 was not included in any analysis, as this patient was announced shortly before recruitment stop and was not randomized. Thus, 9 patients form the main data base of this analysis (panitumumab: 3; control: 4; KRAS mutant: 2). Patient no. 10 (randomized to panitumumab) withdrew his consent to receive chemotherapy “because of an ulcus cruris” and did not present at the scheduled day for treatment initiation.

Tab. 3 Data status

Category	**n**
Number of patients reported to data centre	10
not randomized due to study closure	1*
non-eligible	--
non-evaluable due to completely missing data	--
Evaluable for …	
Baseline characteristics	9
early drop-out (no study treatment)	1**
Course of therapy	8
Study termination	9
Toxicity	8

* Pat. no. 13 ** Pat. no. 10

9.3 GENERAL REMARKS ON THE ANALYSES

In the following analysis results, arm 1 is labelled throughout as “Panitumumab”, arm 2 as “Control” and arm 3 as “KRAS mutant”.

In cases of missing items in individual parameters the sample sizes for specific analyses may deviate from the numbers given in section 9.2. The respective sample size will be provided in these cases. If not stated otherwise, all percentages are calculated with exclusion of missing values.

10 DEMOGRAPHIC AND ANAMNESTIC BASELINE CHARACTERISTICS

10.1 DEMOGRAPHIC CHARACTERISTICS

Mean and median age are presented in Tab. 4. Most patients were of male sex (Tab. 5).

Tab. 4 Age [years]

	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
Mean ± SD	70.3 ± 9	61.8 ± 7	70 ± 1.4	66.4 ± 7.7
Median	75	62	70	69
Quartile	67.5 - 75.5	59 - 64.8	69.5 - 70.5	61 - 71
Range	60 - 76	53 - 70	69 - 71	53 - 76

Tab. 5 Gender

	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
Female	-	2 (50%)	-	2 (22%)
Male	3 (100%)	2 (50%)	2 (100%)	7 (78%)

10.2 ANAMNESTIC CHARACTERISTICS

10.2.1 Tumor history

Two thirds of the primary tumors were located in the colon (Tab. 6). All patients suffered from locally advanced disease at the initial diagnosis (Tab. 7, Tab. 8). The majority of patients (however, not in the panitumumab group) had synchronous metastisation at this time point (Tab. 9). Almost all the tumors were characterized as of intermediate malignancy grade (G2) (Tab. 10). The distribution of KRAS findings corresponds to the protocol requirements (Tab. 11).

Tab. 6 Primary tumor location

Site	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
Colon	2 (67%)	2 (50%)	2 (100%)	6 (67%)
Rectum	1 (33%)	2 (50%)	-	3 (33%)

Tab. 7 pT stage at initial diagnosis

Category	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
T3	1 (33%)	3 (75%)	1 (50%)	5 (56%)
T4	2 (67%)	1 (25%)	-	3 (33%)
TX	-	-	1 (50%)	1 (11%)

Tab. 8 pN stage at initial diagnosis

Category	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
N1	2 (67%)	1 (25%)	1 (50%)	4 (44%)
N2	1 (33%)	3 (75%)	-	4 (44%)
NX	-	-	1 (50%)	1 (11%)

Tab. 9 M stage at initial diagnosis

Category	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
M0	2 (67%)	1 (25%)	-	3 (33%)
M1	1 (33%)	3 (75%)	2 (100%)	6 (67%)

Tab. 10 Grading at initial diagnosis

Grading	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
G2	3 (100%)	3 (75%)	2 (100%)	8 (89%)
G3	-	1 (25%)	-	1 (11%)

Tab. 11 KRAS status

Category	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
MUTANT	-	-	2 (100%)	2 (22%)
WILDTYPE	3 (100%)	4 (100%)	-	7 (78%)

Corresponding to the findings presented in Tab. 9, the median time from initial diagnosis of colorectal cancer to the detection of distant metastasis is 0, but considerably longer in the panitumumab group (Tab. 12). (Small negative values obviously result from histopathological confirmation received only after detection of metastases, in the cases with synchronous dissemination.)

Tab. 12 Time from initial diagnosis to distant metastasis [months]

Parameter	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
Mean ± SD	29.6 ± 36	2.9 ± 5.6	-0.5 ± 0.1	11 ± 23
Median	19.1	0.2	-0.5	0
Quartile	9.5 - 44.4	0 - 3.1	-0.5 - -0.5	-0.1 - 11.3
Range	0 - 69.6	-0.1 - 11.3	-0.6 - -0.5	-0.6 - 69.6

10.2.2 Present tumor status

The sites of distant tumor lesions are presented in Tab. 13. The high number of sites in the control group is due to one case with widely disseminated disease.

Tab. 13 Sites of metastatic lesions at study entry

Site	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
Liver	2 (67%)	4 (100%)	2 (67%)	8 (89%)
Lung	1 (33%)	2 (50%)	1 (33%)	5 (56%)
Pleural	-	1 (25%)	-	1 (11%)
Soft tissue	-	1 (25%)	-	1 (11%)
Lymph nodes	-	2 (50%)	-	2 (22%)
Abdomen	-	1 (25%)	-	1 (11%)
Spleen	-	1 (25%)	-	1 (11%)
Other*	-	1 (25%)	-	1 (11%)

* right pelvis

10.2.3 Performance status

The majority of the patients had an impaired performance status at entry into the trial (Tab. 14). The distribution across the trial groups is in accordance with the findings on metastatic burden.

Tab. 14 Performance status (ECOG/WHO)

Performance status	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
ECOG 0	2 (67%)	1 (25%)	-	3 (33%)
ECOG 1	1 (33%)	1 (25%)	2 (100%)	4 (44%)
ECOG 2	-	2 (50%)	-	2 (22%)

11 STUDY COURSE AND TREATMENT

11.1 EXPOSURE TO STUDY TREATMENT

The duration of study treatment, defined as the time between first application of chemotherapy in cycle 1 and the last date of protocol therapy, is shown in Tab. 15. Overall, the average treatment period was 3 months.

Tab. 15 Duration of study therapy [months]

	Panitumumab	Control	KRAS mutant	Total
n	2	4	2	8
Mean ± SD	2 ± 1.8	2.8 ± 2.2	4.3 ± 1.8	3 ± 1.9
Median	2	3	4.3	3.1
Quartile	1.3 - 2.6	1.2 - 4.6	3.7 - 4.9	1.2 - 4.6
Range	0.7 - 3.2	0.5 - 4.7	3 - 5.6	0.5 - 5.6

With respect to the experimental antibody treatment, patient no. 4 received two cycles and two applications of panitumumab. In patient no. 5, who received five treatment cycles, only 4 doses of the antibody were administered (as one was skipped due to toxicity).

11.2 END OF STUDY TREATMENT

In Tab. 16, the reason for the termination of study therapy is described, with multiple answers possible in a single patient.

Tab. 16 Reason for end of therapy

	Panitumumab	Control	KRAS mutant	Total
n	2	4	2	8
Progression	1 (50%)	2 (50%)	-	3 (38%)
Intolerable toxicity	-	1 (25%)	-	1 (12%)
Patient's wish	-	2 (50%)	-	2 (25%)
Protocol violation	-	-	1 (50%)	1 (12%)
Serious adverse event	1 (50%)	-	1 (50%)	2 (25%)
Investigator's decision	-	1 (25%)	-	1 (12%)

11.3 END OF STUDY PARTICIPATION

The reasons for the individual end of study participation are presented in Tab. 17, with death as the predominant cause.

Tab. 17 Reason for end of study participation

	Panitumumab	Control	KRAS mutant	Total
n	3	4	2	9
Closure of the study	1 (33%)	1 (25%)	-	2 (22%)
Consent to further participation withdrawn	-	1 (25%)	-	1 (11%)
Death	2 (67%)	1 (25%)	2 (100%)	5 (56%)
Other	-	1 (25%)	-	1 (11%)

All death events were reported to be caused by the underlying tumor disease.

12 TREATMENT EFFICACY

Due to the very limited number of patients recruited before study termination, and their distribution among three study arms, no analyses on antineoplastic efficacy have been performed.

13 TOXICITY / SAFETY

13.1 TOXICITY ACCORDING TO NCI CTC

In Tab. 18 to Tab. 20 the maximum NCI CTC toxicity grade for each patient and each specific toxicity is analysed by study group. Both panitumumab patients experienced grade 3 and 4 toxicity.

Tab. 18 NCI CTC toxicity grades (maximum by patient and category): Panitumumab group (n = 2)

Category CTC grade	1	2	3	4
Anorexia	1	--	--	--
Constitutional Symptoms - Other	--	--	1	--
Cough	1	--	--	--
Creatinine	--	--	--	1
Diarrhea	--	1	--	--
Dry skin	1	--	--	--
Dyspnea (shortness of breath)	--	--	2	--
Fatigue (asthenia, lethargy, malaise)	--	1	--	--
Gastrointestinal - Other	1	--	--	--
Hypertension	--	--	1	--
Infection with normal ANC or Grade 1 or 2 neutrophils - Pulmonary/Upper Respiratory - Upper airway	--	1	--	--
Infection with unknown ANC	--	1	--	--
Magnesium, serum-low (hypomagnesemia)	--	--	--	1
Mucositis/stomatitis (clinical exam)	1	--	--	--
Musculoskeletal/Soft Tissue - Other	1	--	--	--
Nausea	2	--	--	--
Neuropathy: sensory	--	1	--	--
Pain - Pulmonary/Upper Respiratory - Chest/thorax	1	--	--	--
Potassium, serum-high (hyperkalemia)	--	--	1	--
Rash: acne/acneiform	--	--	1	--
Urinary frequency/urgency	1	--	--	--
Vomiting	1	--	--	--
Wound complication, non-infectious	1	--	--	--

Tab. 19 NCI CTC toxicity grades (maximum by patient and category): Control group (n = 4)

Category CTC grade	1	2	3	4
Bilirubin (hyperbilirubinemia)	--	--	1	--
Cardiac General	1	--	--	--
Colitis	1	--	--	--
Constitutional Symptoms - Other	--	1	--	--
Dehydration	2	--	--	--
Dermatology/Skin - Other	1	--	--	--
Diarrhea	--	--	2	--
Fatigue (asthenia, lethargy, malaise)	1	--	1	--
Gastrointestinal - Other	1	--	--	--
Hemoglobin	--	1	1	--
Hypertension	1	--	--	--
Infection with normal ANC or Grade 1 or 2 neutrophils -				
Pulmonary/Upper Respiratory - Nose	--	1	--	--
Leukocytes	--	1	--	--
Mucositis/stomatitis (clinical exam)	1	--	--	--
Nausea	2	1	--	--
Neurology - Other	1	--	--	--
Neuropathy: sensory	1	1	--	--
Neutrophils/granulocytes (ANC/AGC)	--	--	1	--
Odor (patient odor)	1	--	--	--
Pain - Musculoskeletal - Back	1	--	--	--
Pain - Pulmonary/Upper Respiratory - Chest wall	--	1	--	--
Platelets	--	1	--	--
Portal vein flow	--	1	--	--
Potassium, serum-low (hypokalemia)	--	--	--	1
Syndromes - Other	1	--	--	--
Vomiting	1	2	--	--

Tab. 20 NCI CTC toxicity grades (maximum by patient and category): KRAS mutant group (n = 2)

Category / CTC grade	1	2	3	4
Cardiac ischemia/infarction	--	1	--	--
Constipation	--	1	--	--
Diarrhea	1	--	1	--
Dyspnea (shortness of breath)	1	--	--	--
Fatigue (asthenia, lethargy, malaise)	1	1	--	--
Hair loss/alopecia (scalp or body)	--	1	--	--
Infection with normal ANC or Grade 1 or 2 neutrophils	--	1	--	--
Nausea	1	--	--	--
Neurology - Other	1	--	--	--
Neuropathy: sensory	1	1	--	--
Ocular/Visual - Other	1	--	--	--
Rash: hand-foot skin reaction	--	1	--	--
Thrombosis/embolism (vascular access-related)	--	--	--	1

13.2 SERIOUS ADVERSE EVENTS

Serious adverse event (SAE) reports were distinctly more frequent in the panitumumab group (Tab. 21). A complete list of all SAEs with details is to be found in appendix 5.

Tab. 21 Incidence of serious adverse events (SAE)

	Panitumumab	Control	KRAS mutant	Total
n	2	4	2	8
Number of patients with SAE	2	2	1	5
Number of SAEs	6	2	3	11

14 DISCUSSION AND CONCLUSIONS

Due to the premature closure of the trial with only nine evaluable patients, distributed across the three study arms, no relevant conclusions can be drawn from this study.

Although the incidence of serious adverse events is numerically higher in the experimental arm in comparison to the chemotherapy only groups, no major unexpected safety problems were detected in these pre-treated patients.

15 REFERENCE LIST

1) Advanced Colorectal Cancer Meta-Analysis Project: Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol. 1992;10(6):896–903.

2) Arkenau T, Schmoll H.-J., Kubicka S et al. Infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus capecitabine plus oxaliplatin (CAPOX) as first line treatment of metastatic colorectal cancer (MCRC): Results of the safety and efficacy analysis. Proc Am Soc Clin Oncol. 2005;23:16, (abstr 3507).

3) Baselga J, Mendelsohn J. Receptor blockade with monoclonal antibodies as cancer therapy. Pharmacol Ther. 1994;64:203-212.

4) Bennouna J, Ducreux M, Hebbar M et al.: Non-inferiority of XELOX versus FOLFOX-6: Efficacy findings from a randomized phase II study of capecitabine + oxaliplatin (XELOX) vs infusional 5-FU/LV + oxaliplatin (FOLFOX-6) as firstline treatment for metastatic colorectal camcer (MCRC). Gastrointestinal Cancer Symposium, ASCO 2007, (abstr 272)

5) Berlin J, et al. Panitumumab therapy with irinotecan, 5-fluorouracil, and leucovorin (IFL) in patients (pts) with metastatic colorectal cancer (mCRC). Ann Oncol. 2004;15 (suppl 13):265a.

6) Boyle, P, Ferlay, J. Cancer incidence and mortality in Europe, 2004. Ann Oncol. 2005;16:481-488.

7) Cassidy et al. XELOX (Capecitabine Plus Oxaliplatin): Active First-Line Therapy for Patients With Metastatic Colorectal Cancer. J Clin Oncol. 2004;22(11):2084-2091.

8) Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008 ,26: 2006-2012.

9) Cunningham D, Pyrhonen S, James RD, et al. Randomized trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure failure for patients with metastatic colorectal cancer. Lancet. 1998;352(9138):1413-1418.

10) Cunningham D, Humblet Y, Sienna S ea. Cetuximab monotherapy plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004;351:337-345.

11) Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A., Bets, D., Mueser, M., Harstrick, A. & Van Cutsem, E.. Cetuximab (C225) alone or in combination with irinotecan (CPT-11) in patients with epidermal growth factor receptor (EGFR)-positive, irinotecan-refractory metastatic colorectal cancer (MCRC). Proc Am Soc Clin Oncol. 2003;22:252 (abstr 1012).

12) Denne JS. Sample size recalculation using conditional power. Statistics in Medicine. 2001;20:2645-2660.

13) De Gramont A, Figer, A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;22:229-237.

14) de Jong KP, Stellema R, Karrenbeld A, Koudstaal J, Gouw AS, Sluiter WJ, Peeters PM, Slooff M, De Vries EG. Clinical relevance of transforming growth factor alpha, epidermal growth factor receptor, p53, and Ki67 in colorectal liver metastases and corresponding primary tumours. Hepatology. 1998;28:971-979.

15) Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. Lancet. 2000;355:1041-1047.

16) Ducreux M, Adenis A, Bennouna J et al. Phase III, randomized, open-label study of capecitabine (X) plus oxaliplatin (XELOX) versus infusional 5-FU/LV plus oxaliplatin (FOLFOX-6) first-line treatment in patients (pts) with metastatic colorectal cancer (MCRC): Findings from an interim safety analysis. Proc Am Soc Clin Oncol. 2005;23:16,(abstr 3596).

17) Ebert M. et al. Aristaless-like homeobox-4 gene methylation is a potential marker for colorectal adenocarcinomas. Gastroenterology. 2006;131:1418-30.

18) EuroQol Group. EuroQol - A new facility for the measurement of health-related quality of life. Health Policy 1990;16 (3):199-208.

19) Gamboa-Dominguez A, Dominguez-Fonseca C, Quintanilla-Martinez L, Reyes-Gutierrez E, Green D, Angeles-Angeles A, Busch, R., Hermannstadter C, Nahrig J, Becker KF, Becker I, Hofler H, Fend F, Luber B. Epidermal growth factor receptor expression correlates with poor survival in gastric adenocarcinoma from Mexican patients: a multivariate analysis using a standardized immunohistochemical detection system. Mod Pathol. 2004;17:579-87.

20) Gold M. Washington Panel on Cost Effectiveness in Health and Medicine. Med Care. 1996;34(12 Suppl):DS197-9.

21) Goldberg RM, et al. A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer; J Clin Oncol. 2004:22:23-30.

22) Grothey A, Deschler B, Kroening H, et al. Phase II study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo) versus weekly high-dose 24h 5-FU infusion/FA + Oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). Proc Am Soc Clin Oncol. 2002;21:129a.

23) Grothey A, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol. 2004 Apr 1;22(7):1209-14.

24) Gullick WJ. Prevalence of aberrant expression of the epidermal growth factor receptor in human cancers. Br Med Bull. 1991;47:87-98.

25) Herbst RS, Shin DM. Monoclonal antibodies to target epidermal growth factor Receptor-positive tumours: A new paradigm for cancer therapy. Cancer. 2002;94:1593-1611.

26) Hecht JR, Patnaik A, Malik A et al. ABX-EGF monotherapy in patients (pts) with metastatic colorectal cancer (mCRC): An updated analysis. Proc Am Soc Clin Oncol. 2004;22:247s. Abstract 3511.

27) Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335-2342.

28) International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2004. http://www.icmje.org/

29) Jemal A, Murray T, Ward, E et al. Cancer statistics, 2005. CA Cancer J Clin. 2005;55:10-30.

30) Kindler HL, Shulman KL. Metastatic colorectal cancer. Curr Treat Options Oncol. 2001;2:459-471.

31) Koehne C, Van Cutsem E, Wils J, et al. Irinotecan improves the activity of the AIO regimen in metastatic colorectal cancer: results of EORTC GI-group study 40986. J Clin Oncol. 2005 .

32) Lachin JM, Foulkes MA. Evaluation of Sample Size and Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification. Biometrics. 1986;42:507-519.

33) Lievre A et al. (2006) KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res. 66,3992-5.

34) Lui, VW & Grandis, JR. EGFR-mediated cell cycle regulation. Anticancer Res. 2002;22, 1-11.

35) Maindrault-Goebel F, Louvet, C, Andre T, et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR. Eur J Cancer. 1999;35:1338-1346.

36) Malik I, Hecht JR, Patnaik A, et al. Safety and efficacy of panitumumab monotherapy in patients with metastatic colorectal cancer. Proc ASCO. 2005;23: 3520 (abstr).

37) Masutti B, Gomez A, Sastre J et al.: Randomized phase III trial of the TTD group comparing capecitabine and oxaliplatin (XELOX) vs oxaliplatin and 5-fluorouracil in continous infusion (FUFOX) as first line treatment in advanced or metastatic colorectal cancer (CRC). Pro Am Soc Clin Oncol. 2006;24:18 (abstr 3580).

38) McLeod HL, McKay JA, Collie-Duguid ES, Cassidy J. Therapeutic opportunities from tumour biology in metastatic colon cancer. Eur J Cancer. 2000;36:1706-1712.

39) Mendelsohn, J. (2001). The epidermal growth factor receptor as a target for cancer therapy. Endocr Relat Cancer. 2001 Mar;8(1):3-9.

40) Meropol NJ, Berlin J, Hecht JR, et al. Multicentre study of ABX-EGF monotherapy in patients with metastatic colorectal cancer. Proc Am Soc Clin Oncol. 2003;22:256 Abstract 1026.

41) Newcombe RG. Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statistics in Medicine. 1998;17(8):873-890.

42) Panitumumab Investigator's Brochure, Version 7.0. Thousand Oaks, CA: Amgen Inc.; June 2007.

43) Panitumumab Clinical Trial Directive Annual Safety Report. Thousand Oaks: Amgen Inc.; August 2005

44) Pfeifer et al. Short-time infusion of oxaliplatin in combination with capecitabine (XELOX $_{30}$) as second- line therapy in patients with advanced colorectal cancer after failure to irinotecan and 5-fluorouracil Annals of Oncology 2006 17(2):252-258.

45) Pazdur R, Coia L, Wagman LD, Ayoub, JP. Colorectal and anal cancers. In: Cancer management: a multidisciplinary approach. Melville, NY: PRR, Inc, 1999:149-175.

46) Porebska I, Hartozinska A, Bojarowski T. Expression of the tyrosine kinase activity growth factor receptors (EGFR, ERB B2, ERB B3) in colorectal adenocarcinomas and adenomas. Tumour Biol. 2000;21:105-115.

47) Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim Results of a Phase III Trial. J Clin Oncol. 2003;21:2059-2069.

48) Rougier P, Van Cutsem E, Bajetta E, et al. Randomized trial of Irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998; 352: 1407-1412.

49) Rowinsky EK, Schwartz GH, Gollob JA, et al. Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. J Clin Oncol. 2004;22:3003-15.

50) Saeki T, Salomon DS, Johnson GR, Gullick WJ, Mandai K, Yamagami K. Association of epidermal growth factor-related peptides and type I receptor tyrosine kinase receptors with prognosis of human colorectal carcinomas. Japan J Clin Oncol. 1995;25:240-249.

51) Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2002;343:905-914.

52) Saltz, L. B., Meropol, N. J., Loehrer, P. J., Sr., Needle, M. N., Kopit, J. & Mayer, R. J. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol. 2004;22, 1201-8.

53) Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol. 1995;19:183-232.

54) Shirai H, Ueno E, Osaki M, Tatebe S, Ito H, Kaibara N. Expression of growth factors and their receptors in human early colorectal carcinomas: immunohistochemical study. Anticancer Res. 1995;15:2889-2894.

55) Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47..

56) Tong WM, Ellinger A, Sheinin Y, Cross HS. Epidermal growth factor receptor expression in primary cultured human colorectal carcinoma cells. Br J Cancer. 1998;77:1792-1798.

57) Tournigand C, Andre T, Achille E et al. FOLFIRI followed by FOLFOX6 of the reverse sequence in advanced colorectal cancer. J Clin Oncol. 2004;22:229-237.

58) Wang HM, Rajagopal S, Chakrabarty S. Inhibition of human colon cancer malignant cell behavior and growth by antisense epidermal growth factor receptor expression vector. Anticancer Res. 1998;18:2297-2300.

59) Yang X-D, Jia XC, Corvalan JR, Wang P, Davis CG, Jakobovits A. Eradication of established tumours by a fully human monoclonal antibody to the epidermal growth factor receptor without concomitant chemotherapy. Cancer Res. 1999;59:1236-1243.

60) Amado RG, Wolf M, Freeman D et al. Analysis of KRAS mutations in patients with metastatic colorectal cancer receiving panitumumab monotherapy. European Journal of Cancer Supplements, Vol 5 No 6, Pa

61) Leventhal BG, RE Wittes: Research methods in clinical oncology. Raven Press, New York, 1988

62) Buyse M: Randomized designs for early trials of new cancer treatments – an overview. Drug Inf J 2000, 34: 387-396

63) Fleming TR: One-sample multiple testing procedure for phase II clinical trials. Biometrics 1982, 38: 143-151

64) Rothenberg M, Cox JV, Butts C et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Ann Oncol. 2008, 19: 1720-1726.

65) Hecht JR, Mitchell E, Chidiac T et al. An updated analysis of safety and efficacy of oxaliplatin (Ox)/bevacizumab (bev) +/- panitumumab (pmab) for first-line treatment (tx) of metastatic colorectal cancer (mCRC) from a randomized, controlled trial (PACCE). ASCO 2008 Gastrointestinal Cancers Symposium (Abstract 273)

66) Rowinsky EK, Schwartz GH, Gollob JA, et al. Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. J Clin Oncol 2004;22:3003-15

67) Vectibix ® EPAR

68) Weiner LM, Belldegrun AS, Crawford J et al. Dose and schedule study of panitumumab monotherapy in patients with advanced solid malignancies. Clin Cancer Res 2008;14(2):502-8