Clinical Study Report

Version/ Date: Report Final Version 1.0 / 28 November 2012

PHASE I/II TRIAL ON THE USE OF CAPECITABINE AND OXALIPLATIN (XELOX) IN COMBINATION WITH BEVACIZUMAB AND IMATINIB IN THE FIRST-LINE THERAPY OF PATIENTS WITH ADVANCED COLORECTAL CANCER

Project code:	AIO-KRK-0205
EudraCT:	2007-000233-18
Short title:	AIO-KRK-0205
Investigational substance:	Capecitabine, Oxaliplatin, Bevacizumab, Imatinib
Reference substance:	N/A
Indication:	Patients with advanced colorectal carcinoma
Study phase:	open-label phase I/ II
Inclusion of first patient:	24.04.2008
End of treatment of last patient:	19.06.2012
Date of final report:	28.11.2012

Sponsor:
Universität zu Köln
Albert-Magnus Platz
50923 Köln

Monitoring:
GSO mbH
Harvestehuder Weg 21
20148 Hamburg

LKP:
PD Dr. med. Ulrich Hacker
Klinikum der Universität zu Köln
Klinik I für Innere Medizin
Kerpener Str. 62
50924 Köln

Principal investigators:
PD Dr. med. Ulrich Hacker
Prof. Dr. med. Thomas Höhler
Prof. Dr. med. Stephan Kanzler
Prof. Dr. med. Thomas Seufferlein/ Prof. Dr. med. Götz von Wichert
Prof. Dr. med. A. Hochhaus/ Dr. med. R.-D. Hofheinz
Dr. med. J. Siebler/ Dr. med. C.-C. Schimanski

GCP statement: This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.
Confidentiality statement: The information provided in this document is strictly confidential

1 SYNOPSIS

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

Trial title: Phase I/II Trial on the Use of Capecitabine and Oxaliplatin (XELOX) in Combination with Bevacizumab and Imatinib in the First-Line Therapy of Patients with Advanced Colorectal cancer

Study centres: A total of 9 study centers participated in this trial. Patients were included at 6 study sites. For a list of investigators and study sites, please refer to Appendix 16.1.4.

Trial duration: Inclusion of first patient: 24.04.2008 End of treatment of last patient: 19.06.2012	**Phase of development:** Phase I/ II
Methodology: Open-label, multi-center phase I/ II	

Trial objectives:

Primary trial objectives phase I:

- Definition of a recommended dose of capecitabine and oxaliplatin with parallel treatment with bevacizumab and imatinib

Primary trial objective phase II:

- Feasibility and tolerability of the dose determined in phase I in the XELOX combination with bevacizumab and imatinib using the methods of determining safety, adverse events and toxicities in combination therapy

Secondary objectives:

- Determining the 6-month progression-free survival rates
- Recording the median time to progression
- Recording the objective response rate (CR and PR)
- Determining the rate of potentially curative resections of metastases
- Recording the time to treatment failure
- Recording the duration of response
- Recording the median survival time

Number of patients: 51

Name of the sponsor:	*Individual study table*	*(For National Authority use only)*
PD Dr. Ulrich Hacker	*Referring to part of the dossier:*	
Name of the finished product:		
Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances:	*Page: N/A*	
Capecitabine, Oxaliplatin, Bevacizumab, Imatinib		

Included in the final evaluation:

Number of patients	**Total**
Recruited	51
Evaluable regarding toxicity	49
Evaluable regarding efficacy	49

Diagnosis and key inclusion and exclusion criteria:

Inclusion criteria:

- Patients with inoperable metastases of histologically proven colorectal cancer
- Measurable tumor parameters in accordance with RECIST criteria. Evaluation of tumor manifestation within 4 weeks of treatment start
- Neutrophil granulocytes ≥ 1,500/µl
- Thrombocytes ≥ 100,000/µl
- Hemoglobin ≥ 9 g/dl or ≥ 5.59 mmol/l (transfusion to achieve or maintain this level is possible)
- Creatinine clearance ≥ 50 ml/min (calculated using Cockroft/Gault), serum creatinine ≤ 1.5 x upper normal limit
- Serum bilirubin ≤ 1.5 x upper normal limit, ALAT and ASAT ≤ 2.5 x upper normal limit, in the event of liver metastases ALAT and ASAT ≤ 5 x upper normal limit
- INR ≤ 1.5 x the upper normal limit
- Written patient informed consent
- Age ≥ 18 years
- General condition: < 2 (ECOG-PS)
- Estimated life expectancy of > 3 months

Excluded medical conditions:

- Previous systemic immunotherapy or chemotherapy, excluding the following:
  - Adjuvant or neoadjuvant treatment of non-metastasized disease which was completed at least 6 months before enrolment in the trial, or within 6 months of end of treatment for adjuvant treatments without progression
- Secondary cancer with the exception of basalioma or successfully treated in situ cancer of the cervix
- Serious internal disease (insufficiently treated arterial hypertension, hemoptysis, heart failure NYHA grades II–IV, symptomatic coronary heart disease, myocardial infarction within one year of enrolment in the trial, serious cardiac arrhythmia requiring treatment, peripheral arterial occlusive disease of stage II or above, uncontrolled serious concomitant disease)
- History of or clinical indication of CNS disease (e.g. primary brain tumor, epilepsy that cannot be sufficiently treated with standard treatment, brain metastases, history of stroke)
- Gastroduodenal ulcer disease or history of chronic inflammatory bowel disease
- Pre-existing polyneuropathy ≥ grade 1 (NCI CTCAE), with the exception of sole absence of tendon reflexes
- Pregnancy, breastfeeding

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

• Any surgery had to have occurred more than 4 weeks before enrolment and a fine needle biopsy more than 1 week before enrolment. Wounds from the surgery had to be completely healed. It was not expected that the patient would have to undergo a major operation during the course of the trial. This excluded any potential resection of liver metastases. If the option for a secondary curative operation, the antibodies was to be discontinued 6 to 8 weeks before surgery. During this time, the patient could continue to receive chemotherapy. Treatment with bevacizumab might be resumed 28 days after surgery, if it is considered medically wise to do so.	• Women of child-bearing potential who have returned a positive or no pregnancy test results at enrolment, post-menopausal women must have had amenorrhea for 12 months in order to be classified as no longer of child-bearing potential • Sexually active men or women (of child-bearing potential) who are insufficiently willing to practice a reliable method of contraception (hormone-releasing IUD coil, hormone injection, hormone implant, abstinence or vasectomy of the male partner, sole use of the pill is not sufficient due to the adverse events, vomiting and diarrhea, associated with treatment) • Known allergies to one of the substances or their active ingredients • Interstitial pneumonia or symptomatic pulmonary fibrosis • Allogenic transplants requiring immunosuppressive treatment • Serious, non-healing wounds, ulcers or bone fractures • Known DPD deficiency • Concomitant treatment with the antiviral sorivudine or its chemical relatives • Previous radiotherapy of the indicator lesion, except in the event of documented progression during radiotherapy and end of radiotherapy at least 4 weeks before enrolment in the trial • Thrombosis or severe bleeding within 6 months of enrolment in the trial (exception: tumor bleeding before the tumor resection surgery) • Hemorrhagic diathesis or tendency towards thrombosis • Anticoagulation therapy (treatment with Marcumar, PTT-affecting heparinisation)

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

- Continual ASA medication > 325 mg/d or regular administration of non-steroidal anti-inflammatories that are known to inhibit thrombocyte function
- Ascites requiring puncture
- Proteinuria with ≥ 1+ in Urin-Stix test, as long as > 1 g protein is detectable in 24-hour total urine
- Simultaneous treatment with preparations containing St. John's Wort
- Consumption of grapefruit juice
- Participation in another trial within 4 weeks of enrolment
- Patients who cannot swallow tablets
- A history of extended drug, medication or alcohol abuse
- Patients who are not in a position to act in accordance with protocol, or who will not, and who cannot or will not undergo treatment or examinations
- Known grade 3/4 allergic reaction to monoclonal antibodies
- Patients who have an interdependency on the sponsor or investigator
- Non-voluntary patients at a mental institution (according to German Drug Law §40(4))
- Patients who lack legal capacity

Treatment duration: Subjects were treated until progressive disease was documented or unacceptable toxicity occurred

Trial medication, dose and method of administration:
Treatment was to be completed in accordance with the following scheme:
Dose level 1:

1.	Oxaliplatin 100 mg/m^2 i.v. for 2 hours, then	Day 1
2.	Bevacizumab 7.5 mg/kg BW i.v. for 90 minutes, or, possibly, over 60 or 30 minutes	Day 1
3.	Capecitabine 2x daily 850 mg/m^2 p.o.	Day 1 (evening) until day 15 (morning)
4.	Imatinib 1x daily 300 mg p.o.	Day 1 until day 21

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

Repetition of the cycle on day 22, treatment duration until progression or until the occurrence of a non-tolerable toxicity.

Dose level 2:

1.	Oxaliplatin 130 mg/m^2 i.v. for 2 hours, then	Day 1
2.	Bevacizumab 7.5 mg/kg BW i.v. for 90 minutes, or, possibly, over 60 or 30 minutes	Day 1
3.	Capecitabine 2x daily 1000 mg/m^2 p.o.	Day 1 (evening) until day 15 (morning)
4.	Imatinib 1x daily 300 mg p.o.	Day 1 until day 22

Repetition of the cycle on day 22, treatment duration until progression or until the occurrence of a non-tolerable toxicity.

6 patients were initially recruited for treatment in the first dose level in the phase I part of the trial. This group experienced a total of three dose-limiting toxicities (DLT): one neurotoxicity, which was considered being related to oxaliplatin, and two patients experienced diarrhea and/or nausea and vomiting. Hospitalization was required in both cases due to dehydration (SAE). Subsequently, three further patients were treated at dose level 1, in accordance with the protocol. No further DLTs occurred.

This meant that the second dose level could be initiated. However, after discussing with the attending physicians and the Independent Data Monitoring Committee (IDMC), dose level 1 was to be used for phase II of the trial. It was expected that an increase in the chemotherapy dose would cause an increased severity in the adverse event diarrhea. The therapy regimen showed a high degree of efficacy in the patients with no disease progression at the date of deciding on a dose level for phase II. An increase in the chemotherapy dose was considered ethically questionable in light of the toxicities that it may entail. For this reason, dose level 1 was established for phase II.

Evaluation criteria:

Primary end point phase I:

- Definition of a recommended dose of capecitabine and oxaliplatin with parallel treatment with bevacizumab and imatinib

Primary end point phase II:

- Feasibility and tolerability of the dose determined in phase I in the XELOX combination with bevacizumab and imatinib using the methods of determining safety, adverse events and toxicities in combination therapy

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

Secondary efficacy criteria:

- Determining the 6-month progression-free survival rates
- Recording the median time to progression
- Recording the objective response rate (CR and PR)
- Determining the rate of potentially curative resections of metastases
- Recording the time to treatment failure
- Recording the duration of response
- Recording the median survival time

Safety

- Adverse event (AEs)
- Serious adverse events (SAEs)

Statistical methods:

The analysis of all parameters was to be done descriptively, giving frequencies, means, medians, ranges and confidence intervals. Explicit p-values were to be given for any explorative statistical tests conducted (e.g. for comparing sub-groups). Generally speaking, the significance level was not to be adjusted with regard to the multiplicity of the analysis, meaning that the p-values reflect an α-error relating to the individual comparison and not relating to the whole experiment. Unless otherwise indicated, two-sided tests were to be used. The statistical methods listed below are generally suitable for the data and distributions common in such trials. The suitability was to be checked after data collection. If necessary, the type of methods to be used was allowed to be modified.

The objective response rate (CR and PR), the rate of potentially curative resections of metastases and toxicity rates were to be compared by manifestation and extent using Fisher's Exact Test, the χ^2 test or the Mantel-Haenszel-Test (or the Cochran/Armitage trend test). Continually distinct data such as laboratory values or dosages were to be analysed using the Wilcoxon test for independent or paired samples.

Data related to events such as overall survival times were to be presented using the life table method by Kaplan/Meier and compared using the log rank test if necessary.

The above-mentioned methods were to be used as required for the univariate analysis of prognostic factors. If a multivariate analysis was required, suitable regression models were to be used (logistic regression, proportional hazard regression model).

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

Interim analysis:

There was to be continual evaluation of toxicity in the phase I part. No formal interim analysis of efficacy parameters for a previously established period had been planned. The data were to be analysed at regular intervals, including in phase II, with regard to serious toxicities and the results presented to the trial management organization.

Summary:
A total of 51 patients were included in the study. Two of these 51 patients were classified “non-eligible” by the LKP before analysis due to serious protocol violations. For 49 patients, analysis of efficacy and safety was done.

Demographic data and baseline data:

Demographic and baseline data were generally analysed of the 49 patients, when available.

The median age was 65 years. 76% of the patients were men.

More than half of the patients suffered from colon carcinoma. The percentage of patients with rectum carcinoma was 40%.

TNM classification was done for 45 patients. For almost three quarters of them, the pT stage at the initial diagnose was stated as pT3, for further 13% pT4. In 41%, lymph nodes were not affected. About half of the patients showed distant metastases.

The organs mainly affected by metastases were lung, liver and lymph nodes. The percentage of patients with only one affected organ was 24%.

61% of the patients showed an unrestrained general condition at the time of inclusion with an ECOG of 0. With a median value of 130 mmHg for the systolic and 80 mmHg for the diastolic value, the blood pressure pointed no further abnormalities.

80% of the patients had been operated on the primary tumor and 4% of the patients with rectum carcinoma were radiated pre- and post-operatively, respectively. Less than one fifth of the patients had received adjuvant chemotherapy before.

Regarding the lab values, in view of the evaluation of the prognostic score according to Köhne, only the leukocytes and the alkaline phosphatase values were analysed. The numbers of leukocytes extended to a large range, though more than half of the patients belonged to the lower one (< 8.0 x10^3/µl) of the prognostic categories. Regarding alkaline phosphatase, only 8% of the patients showed considerably increased values of ≥ 300 U/l.

The prognostic score according to the publication of Köhne et al. was evaluated by means of all baseline data. In this score, one point is given for each increased leukocytes (< 8000 /µl), increased alkaline phosphatase (> 300 U/l), the existence of two or more metastases and a bad general condition (ECOG > 1), resulting in a score from 0 to 4. The distribution showed that 48% of the analysed patients had reached 1 point, followed by 29% with 2 points. Stratification of risk

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

into the categories “low risk” (0-2 points) and “high risk” (3-4 points) proved usefully only to a limited extent, as the “high risk” group was only filled with 3% of the patients. One reason was that because of the inclusion criterion “ECOG < 2” a score of 4 points could not be reached.

Efficacy results:

Time to progression (TTP)

The time to progression was analysed using Kaplan-Meier estimate. All 49 eligible patients were included in the evaluation, for 31 of these patients, the date of death was documented at the time of analysis.

The median TTP was 10.6 months (95% confidence interval: 9.5 … 15.8). The progression-free survival after one year is 40% (95% confidence interval: 28 … 56%), within two years, almost all patients are progressive again.

Progression free survival (PFS) after 6 months

The analysis of the PFS after 6 months was done for the purpose of a sensitivity analysis. The number of 37 patients who were documented and progression-free after 6 months was referred to

- all included patients, including the patients classified as “non-eligible” (n = 51)
- the eligible patients, ITT (n = 49)
- the patients with duration of treatment of at least two cycles and appropriate monitoring, PP (n = 45)

In addition, a Kaplan-Meier estimate was performed (n = 49). The analysis was affected marginally by the fact that one patient without progression within the first 6 months was censored.

With the exception of the first estimate (related to n = 51 patients, 6-months PFS = 73%), all other rates lay above the requirement that was prospectively defined as “promising” of 75%. The results were 76%, 77% and 82% for the ITT population (n = 49), the Kaplan-Meier estimate (n = 49) and the PP population (n = 45), respectively. Hence, the outcome of the study can be considered positively.

Response rate (RR)

All subsequent statements are related to the “best response”, i.e. the best response category that was reached during the study period. Referring to the ITT population (n = 49), 21 (43%) and 20 (41%) patients achieved PR and SD, respectively, as best response. For 4 patients, the response was not reported, one patient reached CR. The rate of non-responders was small.

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

A total of 22 patients achieved an objective remission (CR + PR). For the purpose of a sensitivity analysis, this number was related to different populations:

- With respect to the PP population (n = 45), an objective remission rate of 49% occurred.
- With respect to the ITT population (n = 49), the objective remission rate was 45%.

These results rather lay at the lower end of the achievable that can typically be reached with the current combination therapies of metastasized colorectal carcinoma in the first-line therapy.

The duration of response in the 22 patients with objective remission rate was 15.5 months.

Overall survival (OS)

49 patients treated in this study were included in the analysis of OS. By the time of analysis, 31 deaths were documented. The Kaplan-Meier estimate was used as evaluation method.

The median OS was 23.2 months (95% confidence interval: 18.8 … 31.1 months). The one-year survival rate was 86% (95% confidence interval: 76 … 96%), the two-years survival rate was 49% (95% confidence interval: 37 … 66%)

Toxicity results

Adverse Events (AEs)

Most adverse events occurred in a mild to moderate form, only 3 cases of AE grade 4 (one endocrine event, one ileus and one hypokalemia) were reported.
Hematotoxicity mainly affected the white blood cell count and was observed only in individual cases in grade 3. Myelosuppression grade 4 did not appear, febrile neutropenia or severe infections affected only two patients. Relevant thrombocytopenia and bleeding were rare.
Gastrointestinal side effects were observed frequently. Thereby, nausea, vomiting and diarrhea dominated.
Neurotoxicity caused by oxaliplatin was severe in about three quarters of the patients.
Hypertension associated with bevacizumab was reported for only 14% of the patients and was only developed in a mild form.
The majority of the patients suffered from fatigue; however, this is a common observation in patients with a metastasized tumor receiving combination chemotherapy.
As expected, hand-foot syndrome caused by capecitabine was one of the main toxicities. It was observed in 43% of the patients, but a severe form was only reported in two cases.
A disposition of relationship of adverse events to study medication was not contained in the biometric report of WiSP GmbH.

Name of the sponsor: PD Dr. Ulrich Hacker	*Individual study table* *Referring to part of the dossier:*	*(For National Authority use only)*
Name of the finished product: Xeloda®, Eloxatin®, Avastin®, Glivec®	*Volume: N/A*	
Name of the active substances: Capecitabine, Oxaliplatin, Bevacizumab, Imatinib	*Page: N/A*	

Serious Adverse Events (SAEs)

A total of 36 serious adverse events in 21 patients were reported, whereof 20 were considered to be related to study medication, 14 were attributed to the seriousness of the underlying disease and for 8 events, a possible cause of the event other than study medication, the pre-existing/underlying disease, another treatment or protocol-related procedures was given.
Two SUSARs were reported during the course of the study: “Hypophysial hemorrhage” and “pancreatic cancer”. However, none of the trial-related experiences revealed a new safety issue concerning the use of the investigated medications in patients with colorectal cancer.

Date of report: 28.11.2012