Summary Report

FOR

THE CLINICAL TRIAL

A randomized, placebo-controlled, multicenter phase II study to investigate the protectivity and efficacy of Metformin in combination with FOLFIRI and Cetuximab in subjects with previously untreated, K-RAS wild type, metastatic colorectal cancer

EudraCT No.: 2011-001010-34

INVESTIGATIONAL MEDICINAL PRODUCT(S):	**Metformin**
INDICATION:	**Colorectal cancer**
PHASE OF STUDY	**Clinical Phase II**
STUDY INITIATION DATE:	**23 April 2012**
STUDY COMPLETION DATE:	**10 February 2014**
SPONSOR:	**Austrian Breast & Colorectal Cancer Study Group**

Declaration: Above mentioned clinical Trial was conducted in compliance with Good Clinical Practices (including the archiving of essential documents), Declaration of Helsinki and regulatory requirements.

1 Overview

Title of Study:
A randomized, placebo-controlled, multicenter phase II study to investigate the protectivity and efficacy of Metformin in combination with FOLFIRI and Cetuximab in patients with previously untreated, K-RAS wild type, mCRC.

General remarks:
Recruitment for this study was prematurely stopped due to slow accrual. The treatment period according to the protocol for all recruited 8 patients was completed due to ethical reasons and the end of study was newly defined with the last visit of the last patient (= end of treatment visit = end of study visit) planned at the end of January 2014. The follow up visits for all other enrolled patients were planned until the timepoint of this last visit of the last patient. The safety reporting until 14 days after last investigational medical product (IMP) administration according to protocol remained unchanged.

Study Center(s): 8 Austrian sites of which 4 enrolled patients

Publications:
- No publication available

Phase of Development: II

Studied Period (years): 23.04.2012 – 10.02.2014
- date of first enrolment: 25.04.2012 First Patient in
- date of last completed: 05.11.2013 Last Patient out

2 Objectives

The primary objective of the study was:
- the reduction in chemotherapy-associated steatosis in subjects with first-line palliative treatment of metastatic colorectal cancer (mCRC)

The secondary objectives of the study were:
- to evaluate the safety and tolerability of Metformin in combination with Folinic acid + Fluorouracil + Irinotecan (FOLFIRI) and Cetuximab as first line therapy for Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) wild-type mCRC by recording the adverse events and abnormal laboratory values associated with the study treatments
- to assess the efficacy of Metformin in combination with FOLFIRI and Cetuximab as first line therapy for KRAS wild-type mCRC with respect to tumor response rate, progression free survival and overall survival
- the reduction in chemotherapy-associated steatohepatitis in subjects with first-line palliative treatment of mCRC

3 Study Design

This study was designed as a randomized, placebo-controlled, double-blind, multicenter, parallel group phase II trial with 106 first-line subjects with metastatic KRAS wild type CRC. Subjects with histologically confirmed, KRAS wild-type CRC without previous chemotherapy for metastatic disease were screened for this study. Approximately 10 sites in Austria were planned to participate in the study. Subjects were randomized with a web-based randomization system (Randomizer) according to a ratio of 1:1 into two groups:
- Group A: FOLFIRI + Cetuximab + Metformin every 2 weeks for 12 cycles
- Group B: FOLFIRI + Cetuximab + Placebo every 2 weeks for 12 cycles

The study consisted of the following periods: screening period, treatment period (24 weeks), Follow-up period (with visits every 6 months for a maximum of 2 years after end of treatment visit of the subject).
A Data Monitoring Committee (DMC) was established to evaluate Patient Safety. The responsibility of the DMC was to evaluate deviations of medical relevance and safety issues.

4 Target Patient Population and Sample Size

The sample size was calculated for the primary objective. Data from literature indicated that for patients without first-line palliative treatment of mCRC (placebo group) about 40% of subjects would experience steatosis. A sample size of 53 in each treatment group (106 subjects in total) was calculated to be necessary to detect a significant difference of at least 23%-points (i.e. 17% steatosis in the Metformin group; Odds Ratio=0.31) at a one-sided alpha of 0.05 with a power of 80%, using a log odds ratio test. Assuming a drop-out rate of about 20%, a maximum of 132 subjects were planned to be enrolled to achieve 106 evaluable subjects with wild-type KRAS (53 subjects on Metformin, 53 on placebo). No replacement of subjects was allowed.

Based on these results one interim analysis for futility after the evaluation of 50% of the patients (54 evaluable patients) and in addition two safety analyses for evaluation of reported adverse events between the two treatment groups at two different timepoints (20/54 evaluable patients) were planned. In order to control the overall type I error at the 5% level, the interim analysis would have followed a Lan-DeMets alpha-spending approach, using an O'Brien-Fleming boundary function.

5 Blinding

The generation of the unblinded IMP allocation list via the randomization system was conducted externally at the Medical University of Vienna. In addition, the unblinded IMP allocation list was provided to an external trial pharmacist to arrange for shipment of adequately labelled, blinded IMP to the site. The randomization was completed after provision of a blinded IMP code to the site. An automatically generated confirmation of the blinded IMP code was sent to the randomizing person via email. A detailed description about the randomization process was provided to the sites.

6 Diagnosis and Main Criteria for Inclusion

Inclusion criteria

1. signed written informed consent
2. male or female
3. at least 18 years of age
4. diagnosis of histologically confirmed, KRAS wild-type adenocarcinoma of the colon or rectum
5. non-resectable metastatic colorectal carcinoma
6. either presence of at least one liver lesion measurable unidimensionally by CT scan or MRI or at least one resectable liver metastasis with non-resectable extrahepatic disease (as assessed within 3 weeks prior to randomization)
   Subjects with non-resectable metastases were defined as: technically non-resectable (local surgeon in cooperation with local radiologist will define non-resectability on the basis of remaining functional liver tissue, infiltration of all liver veins, infiltration of both liver arteries, both portal branches or both bile ducts)
7. Subjects scheduled to receive Cetuximab and FOLFIRI
8. ECOG performance status 0 - 1 at study entry
9. Leukocytes ≥ 3.0 x 10^9/L and neutrophils ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, and hemoglobin ≥ 8 g/dL Bilirubin ≤ 1.5 x upper limit of normal (ULN), aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) ≤ 5 x ULN

Exclusion criteria

1. brain metastasis (if suspected, brain scan indicated)
2. previous chemotherapy for the currently existing metastatic disease
3. known or newly diagnosed diabetes
4. subjects with acute coronary syndrome (ACS) within the last three months
5. stage 3 or 4 heart failure defined according to the New York Heart Association (NYHA) criteria
6. uncontrolled angina
7. contraindications to Metformin (renal impairment [epidermial growth factor receptor (EGFR) <45 mL/min/1.73m^2], known hypersensitivity to Metformin, acute illness [dehydration, severe infection, shock, acute cardiac failure]), and suspected tissue hypoxia

8. Surgery (excluding diagnostic biopsy, central venous catheter) or irradiation within 2 weeks prior to study entry defined as given written informed consent
9. concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol
10. administration of any investigational agent(s) within 4 weeks prior to study entry
11. previous exposure to EGFR-pathway targeting therapy
12. acute or sub-acute intestinal occlusion or history of inflammatory bowel disease
13. known grade 3 or 4 allergic reaction to any of the components of the treatment
14. any concurrent malignancy other than non-melanoma skin cancer, or carcinoma in situ of the cervix (subjects with a previous malignancy but without evidence of disease for ≥5 years will be allowed to enter the trial)
15. pregnancy or lactation
16. inadequate contraception (male or female subjects) if of childbearing or procreative potential
17. known drug abuse/ alcohol abuse
18. legal incapacity or limited contractual capacity
19. medical or psychological condition which in the opinion of the investigator would not permit the subject to complete the study or sign meaningful informed consent.

7 Study Treatment

Investigational Medical Product

The supplied IMP was provided as tablets of identical appearance containing placebo or 500 mg Metformin hydrochloride corresponding to 390 mg Metformin base. Labelling and packaging of the IMP was conducted according to Good Manufacturing Practice (GMP), Good Clinical Practice (GCP), and any local or national regulatory requirements. The IMP was provided in a bottle containing 30 tablets. Each medication box containing IMP had a label specifying the study protocol number and the kit number. The study sites were supplied with study medication free of charge by Merck, Austria.

IMP (Metformin/Placebo) was given twice daily throughout the chemotherapy until the end of the treatment period. The starting dose of IMP administered as Glucophage® was 500 mg p.o. twice daily for 7 days (daily dose 1000 mg p.o.). The dose was increased to 1000 mg p.o. twice daily at day 8 (daily dose 2000 mg p.o.) unless no toxicity ≥ grade 2 due to IMP occurred. The total duration of treatment was 12 cycles (=24 weeks).

Non-investigational Medical Product

Approved/indicated non-investigational medical products (NIMP) (FOLFIRI/Cetuximab) were given for 12 cycles (= 24 weeks).

Folinic acid
Route of administration: i.v. infusion
Dose: folinic acid 400 mg/m² as a 2-hour i.v. infusion every 2 weeks

5- fluorouracil
Route of administration: i.v. bolus/infusion
Dose: i.v. bolus 5-FU 400 mg/m², followed by FU 2400 mg/m² over 46 hours i.v. infusion every 2 weeks

Irinotecan
Route of administration: i.v. infusion
Dose: Irinotecan 180 mg/m² as a 90 min i.v. infusion every 2 weeks

Cetuximab
Route of administration: 2-hour i.v. infusion (infusion rate must never exceed 10 mg/min = 5 ml/min)
Dose: Cetuximab 500 mg/m² as a 2-hour i.v. infusion every 2 weeks

8 Examinations

Response to treatment was assessed every 8 weeks based on imaging, i.e. three times during treatment and once at baseline. In addition, a liver biopsy of hepatic metastasis and normal liver tissue was planned before the first cycle and at the end of treatment after 12 cycles of chemotherapy. Further details can be found in Figure 1.

Figure 1: Flowchart

	Screening / Baseline		Treatment Phase			Follow-up Phase	
	Within 14 days before randomisation	**After randomisation but prior to first therapy**	**At each visit**	**Every 8 weeks**	**End of treatment visit (24 weeks)**	**Follow-up every 6 months**	**End of study visit (last FUP-visit)**
Informed consent	x[4]						
Tumour imaging (CT or MRI scan) and staging	x[5]			x	x		
Demographic data	x						
Medical history	x						
Inclusion/exclusion criteria	x[6]						
Liver biopsy		x[7]			x		
Performance status	x			x	x		
Weight and BSA	x		x				
ECG	x				x		
Blood sampling for clinical chemistry[1]	x		X[8]		x		
Blood sampling for hematology[2]	x		X[8]		x		
Additional blood sampling[3]	x			x	x		
Pregnancy test[11]	x (blood test)		x (monthly) (urin)		x		
Evaluation/documentation for resectability of liver metastases				x	x	x	
(Serious) adverse events			x		x	x	x
Concomitant medication[10]			x		x		
Survival status					x	x[9]	x[9]
IMP		Twice daily					

Legend: [1] bilirubin, ASAT, ALAT, serum creatinine, potassium, lactate, glucose; [2] hemoglobin, white blood cell count, platelet count, differential blood count; [3] CEA, eGFR, magnesium, HbA1c, insulin and blood sampling for genomic polymorphisms (only once at Screening/Baseline); [4] must be signed prior any study-specific procedure; [5] within 3 weeks prior to randomisation; [6] Brain scan if indicated; [7] prior to first therapy; [8] on day 1 of each cycle; [9] only IMP related (S)AEs; [10] For serious adverse events and adverse events, which are IMP-related (defined as likely and definitely related), concomitant medication will be recorded in the CRF; [11]all pre- and perimenopausal females except patients with hysterectomy

9 Criteria of Evaluation

Assessment of reduction in chemotherapy-associated steatosis due to treatment with FOLFIRI/Cetuximab combined with Metformin compared to treatment with FOLFIRI/Cetuximab combined with Placebo, measured by the steatosis sub-score of the non-alcoholic fatty liver disease (NAFLD) activity score.

Safety was documented by assessing the adverse events according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) criteria, version 4.0.

10 Statistical Methods

The primary endpoint was defined as the reduction of chemotherapy-associated steatosis due to treatment with FOLFIRI/Cetuximab combined with Metformin compared to treatment with FOLFIRI/Cetuximab combined with Placebo, assessed by the steatosis sub-score of the NAFLD activity score (NAS). It was planned to be evaluated after the last treatment visit, i.e. after the second biopsy and should be performed on an intention-to-treat basis (ITT). The ITT population would have included all randomized subjects except those subjects who withdrew informed consent and the permission to use their data collected by then, and who were evaluable according to the primary endpoint. The proportions of subjects exhibiting steatosis (sub-score of NAS 2-3) were to be compared between treatment arms (verum vs placebo) using the one-sided log odds ratio test.

Demographic and anamnestic data at baseline were intended to be checked for differences between the two treatment arms at a two-sided 5% significance level to detect heterogeneities. The same was planned to be done for steatosis at baseline. Variables showing statistically significant differences between the treatment arms at baseline were planned to be included in a multiple logistic regression model to remove their effects on the primary endpoint.

Secondary endpoints included progression free survival (PFS), overall survival (OS), safety / adverse events, objective response rate (complete response (CR) / partial response (PR)) as assessed by response evaluation criteria in solid tumours (RECIST) criteria version 1.1. and reduction in chemotherapy-associated steatohepatitis as assessed by NAS.

However, analyses were not performed as the trial was prematurely terminated after randomization of only 8 patients.

11 Patient Disposition and Demography

8 patients (2 female and 6 male) with a median age of 61 (35 to 78) were included in the study prior to the early study termination. While there were 4 patients with colon cancer (2 with T3, 2 with T4; 1 with N0, 2 with N1, 1 with N2; 3 with grade 2, 1 with grade 3), 3 patients had rectum cancer (2 with T3, 1 with Tx; 1 with N1, 2 with Nx; all 3 with grade 2) and for 1 patient primary tumor classification was not done.

12 Summary of efficacy results

As the trial was prematurely terminated after randomization of 8 patients, the planned efficacy analysis (including 1 interim efficacy analysis) could not be conducted.

For 4 patients steatosis was assessed by NAS at screening. 2 of them showed NAS of 0, the other 2 a NAS of 1. Radiological assessments for steatosis throughout the study were only available for 1 patient who did not have a screening NAS assessment. According results are shown in Table 1.

Table 1: Steatosis Radiological Assessment

Subject	Treatment	Cycle	Steatosis	Density Liver	Density Spleen
2	Placebo	Screening/Baseline	yes	145	123
2	Placebo	Cycle 4	yes	127	124
2	Placebo	Cycle 8	yes	135	143
2	Placebo	End of Treatment	yes	133	127

Evaluation of metastases was possible for 7 patients at Cycle 4 (Table 2) and for 4 patients at Cycle 8 (Table 3).

Table2: Metastases Evaluation Cycle 4

Subject	Sum Target Lesion (mm)	Location	Liver Location	Size
1	64	Liver	segment VII	36
			segment IVa	8
		Lung		20
2	98	Ascites in the Douglas		.
		Liver	segment II	52
			segment V	38
			multiple metastases	.
		Lymph nodes, caudal of the aor		0
		Lymph nodes, mesenterial		.
		Lymph nodes, paraaortal left		8
3	32	Liver	right liver lobe	0
			left liver lobe	24
			left liver lobe	8
4	140	Liver	segment II	31
			segment IVa	36
			segment VI	23
			segment V	27
			segment VII	23
5	215.3	Liver	segment II	49.4
			segment III	41.2
			segment IVb	45.5
			segment I	38.9
			segment VII	40.3
6	456.3	Liver	segment II	82
			segment IVa	111
			segment V	102
			segment VI	58.3
			segment VII	103
7	340.7	Liver	segment II	54.4
			segment IVa	64.9
			segment IVb	72.6
			segment V	71.1
			segment VI	77.7

Table 3: Metastases Evaluation Cycle 8

Subject	Sum Target Lesion (mm)	Location	Liver Location	Size
1	64	Liver	segment VII	33
			segment IVa	11
		Lung		20
2	76	Liver	segment II	35
			segment V	34
			multiple liver metastases	.
		Lymph nodes, caudal of the aor		0
		Lymph nodes, mesenterial		.
		Lymph nodes, paraaortal left		7
		ascites in the Douglas		.
3	22	Liver	right liver lobe	0
			left liver lobe	14
			left liver lobe	8
4	116	Liver	segment II	23
			segment IVa	39
			segment VI	29
			segment V	23
			segment VII	2

13 Summary of safety results

As the trial was prematurely terminated after the randomization of 8 patients, the planned safety analysis (including two interim safety analyses) could not be conducted.

For the 8 patients participating in the study none of the reported serious adverse events (SAEs) was assessed as related to the IMP. Furthermore, none of the reported SAEs was assessed as related to liver biopsy. No predefined biopsy–related SAE occurred during the conduct of the study. Therefore, no actions for safety reasons were taken.

3 patients died during the conduct of the study – 2 due to primary carcinoma and 1 due to pulmonary embolism. Progression of the underlying disease was not regarded as SAE per protocol. For the patient suffering from pulmonary embolism the event was neither assessed as related to the study medication, nor was there a causal relationship to the liver biopsy.

14 Conclusion

Due to the premature termination of the study, no safety or efficacy conclusions can be drawn from the study setting. Efficacy as well as safety outcomes are solely descriptive and do not allow for a comprehensive, valid analysis of the trial.