Clinical Study Report - Synopsis

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A CONTROLLED RANDOMIZED DOUBLE-BLIND PHASE II STUDY OF FOLFOX6 OR FOLFIRI COMBINED WITH SORAFENIB VERSUS PLACEBO IN SECOND-LINE METASTATIC COLORECTAL CARCINOMA (CRC)

Project code:	AIO KRK 0307
EudraCT:	2008-000803-26
Short title:	**FO**LFOX6/FOLFIRI plus **S**orafenib in second-line **Co**lorectal cancer (FOSCO)
Investigational substance:	FOLFOX/FOLFIRI in combination with sorafenib
Reference substance:	FOLFOX/FOLFIRI in combination with placebo
Indication:	Metastatic colorectal carcinoma
Study phase:	Phase II
Inclusion of first patient:	28.04.2009
Recruitment stop:	08.09.2011
End of treatment of last patient:	18.07.2012
Date of final report Version 1.0:	16.04.2013

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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

SYNOPSIS

Name of the sponsor: AIO-Studien-gGmbH	*(For National Authority Use only)*
Name of the finished product: Nexavar®	
Name of the active substances: Sorafenib	
Name of marketing authorization holder: Bayer AG	

Trial title: A Controlled Randomized Double-Blind Phase II Study of FOLFOX6 or FOLFIRI Combined with Sorafenib Versus Placebo in Second-Line Metastatic Colorectal Carcinoma (CRC)

Study centres: A total of 51 sites in Germany participated in this trial. Patients were included at 28 study sites.

Studied period:	**Phase of development:**
Inclusion of first patient: 28-Apr-2009 End of treatment of last patient: 18-Jul-2012	Phase II

Trial objectives:

Primary trial objective:

- To compare the progression-free survival (PFS) between patients receiving chemotherapy (FOLFOX6 or FOLFIRI) + sorafenib with chemotherapy + placebo

Secondary objectives:

- Disease control rate
- Response rates
- Overall survival (OS)
- Growth modulation index (change of TTP2/TTP1 ratio)
- Safety

Methodology: Controlled, randomized, double-blind, multi-center phase II trial
Patients were randomized centrally in a ratio of 1:1 to FOLFOX6/FOLFIRI plus sorafenib or FOLFOX6/FOLFIRI plus placebo. Patients who had received an oxaliplatin-based fluoropyrimidine-containing regimen in first-line would obtain FOLFIRI during this study. Patients who had received an irinotecan-based fluoropyrimidine-containing regimen in first-line would obtain FOLFOX6. Chemotherapy was administered Q2W. Sorafenib/placebo were administered on days 2-12 of each cycle. Patients were treated until disease progression , intolerability of therapy, withdrawal of consent, or death. Response or progression of disease were measured by CT or MRI using RECIST criteria V1.0.

Number of patients:
Planned: 240 – Enrolled: 101 – Analysed: 97

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Diagnosis and main inclusion and exclusion criteria

Main Inclusion criteria:

- Age ≥ 18 years
- ECOG Performance Status of 0 to 2
- Life expectancy of at least 12 weeks
- Subjects with at least one uni-dimensional (RECIST) measurable lesion of metastatic colorectal carcinoma after first-line chemotherapy with an oxaliplatin- or irinotecan-based, fluoropyrimidine-containing regimen ± bevacizumab and a progression subsequently. Lesions measured by CT-scan or MRI
- Adequate bone marrow, liver and renal function as assessed within 7 days prior to screening
- Signed and dated informed consent before the start of specific protocol procedures

Main Exclusion Criteria:

- History of cardiac disease: congestive heart failure >NYHA class 2; active CAD (MI more than 6 mo prior to study entry is allowed); cardiac arrhythmias requiring antiarrhythmic therapy (beta blockers or digoxin are permitted) or uncontrolled hypertension
- History of HIV infection or chronic hepatitis B or C
- Active clinically serious infections (> grade 2 NCI-CTC version 3.0)
- Symptomatic metastatic brain or meningeal tumors (unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry and is clinically stable with respect to the tumor at the time of study entry)
- Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors [Ta, Tis & T1] or any cancer curatively treated > 3 years prior to study entry

Treatment duration: Patients were treated until progression, intolerability of therapy, withdrawal of consent, or death. Treatment duration ranged from 1.0 to 11.9 (median 3.6) months in the sorafenib arm and from 1.0 to 11.0 (median 4.0) months in the placebo arm.

Trial medication, dose, method of administration, batch numbers:
Sorafenib and placebo were investigational medicinal products.

Batch# blinded IMP	Batch# sorafenib 200mg	Batch# placebo
032009	R29801	P14103/BX02KSP1
102010	T11401	T11402

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Doses:
Sorafenib 400 mg PO bid (2x2 tbl.) on days 2-12, OR
Placebo 2 tbl. PO bid on days 2-12.
FOLFIRI and FOLFOX are standard treatments. Thus, 5-fluorouracil, leucovorin, oxaliplatin and irinotecan were background medication and sourced by study sites.
FOLFOX6:
Oxaliplatin 100 mg/m^2 dissolved in 500 ml Glucose 5% solution IV (120 min) on day 1
Leucovorin 400 mg/m^2 dissolved in 100 ml NaCl 0.09% solution IV (30 min) on day 1
5-FU 400 mg/m^2 IV bolus (2-4 min) on day 1
2400 mg/m^2 dissolved in 500 ml NaCl 0.09% solution (46 hour infusion) on day 1-2
FOLFIRI:
Irinotecan 180 mg/ m^2 dissolved in 250 ml NaCl 0.09% solution IV (120 min) on day 1
Leucovorin 400 mg/m^2 dissolved in 100 ml NaCl 0.09% solution IV (30 min) on day 1
5-FU 400 mg/m^2 IV bolus (2-4 min) on day 1
2400 mg/m^2 dissolved in 500 ml NaCl 0.09% solution (46 hour infusion) on day 1-2
Cycles were repeated on day 15 (= day 1 of consecutive cycle, Q2W treatment)

Endpoints
Primary endpoint: Progression-free survival
Secondary endpoints:
Efficacy:
- Overall survival
- Response rates
- Disease control rate
- Growth modulation index (change of TTP2/TTP1 ratio)

Safety:
- Adverse events (AEs)
- Serious adverse events (SAEs)

Statistical methods:
The statistical assumption was that patients who receive FOLFOX6 or FOLFIRI in second-line therapy show a median PFS of 4.5 months. It was estimated that sorafenib might increase PFS by about 45% to 6.5 months.
With an alpha error (one-sided) of 0.05 and a power of 80% 186 PFS events are required. The total number of patients was to be 240 taking approximately 5% invalidity rate into account, assuming an accrual time of 18 months and subsequent follow-up of 6 months.
The primary endpoint PFS was analyzed using a stratified log rank test with a one-sided alpha of 5%. Stratification was performed by parameters FOLFOX vs. FOLFIRI; bevacizumab vs. no bevacizumab in first-line therapy; and ECOG PS 0/1 vs. ECOG PS 2.

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Changes to the conduct of the study

Due to slow recruitment, the clinical trial was about two years behind schedule. Recruitment would have needed another 17 months to reach 240 patients. Moreover, the protocol excluded patients who were pre-treated with cetuximab and other EGFR-reactive antibodies, a standard therapy provided to patients with wild type KRAS status, leading to a strong selection bias for patients with RAS mutant tumors. Hence, it was decided to stop recruitment after 101 patients. Prior to study termination, protocol version 1 was amended to version 2.2 (18.06.2010). The original version of the protocol stated the necessity of a confirmatory tumor assessment according to RECIST 1.0 after 4 weeks. “To be assigned the status of a partial or complete response, changes in tumor measurement must be confirmed by repeat assessments that should be confirmed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate”. In order to avoid unnecessary CTs for the patients and protocol violations for participating sites, confirmatory tumor assessment was moved to the next regular assessment at 8 weeks.

Changes to planned analyses

Due to premature study discontinuation, overall sample size was too sparse to perform all pre-planned statistical analyses. Therefore, the Clinical Trial Director decided to conduct an abbreviated statistical analysis focusing on those issues deemed to be most relevant.

RESULTS

Number of patients, Demographic and baseline data, and analysis sets:

101 patients were recruited. 49 were randomized to sorafenib treatment and 52 to placebo. Only 45 patients were actually treated with sorafenib, hence the full analysis set (FAS) as well as the safety set contain 45 pts in the sorafenib arm and 52 pts in the placebo arm. The per protocol set contains 33 sorafenib-treated pts and 44 pts who received placebo. See Table 1 for further baseline data

N (%)	**Sorafenib** N = 49	**Placebo** N = 52	**Total** N = 101
FOLFIRI	26 (53.1%)	30 (57.7%)	56 (55.4%)
FOLFOX6	19 (38.8%)	22 (42.3%)	41 (40.6%)
Female	13 (28.9%)	15 (28.8%)	28 (28.9%)
Male	32 (71.1%)	37 (71.2%)	69 (71.1%)
Age Median (Min., Max.)	61.8 (33, 80)	64.1 (29, 80)	63.0 (29, 80)
ECOG 0	23 (51.1%)	34 (65.4)	57 (58.8%)
ECOG 1	20 (44.4%)	17 (32.7%)	37 (38.1%)
ECOG 2	3 (6.1%)	1 (1.9%)	4 (4.0%)
Bevacizumab pre-treatment	33 (67.3%)	37 (71.2%)	70 (69.3%)
No bevacizumab pre-treatment	16 (32.7%)	15 (28.8%)	31 (30.7%)

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Efficacy results:

Primary end point: PFS

Progression-free survival (PFS) was similar between both treatment arms for the full analysis set. Progression events observed were 42 in the sorafenib arm and 43 in the placebo arm. Median PFS was 5.2 [90% CI 3.8-6.4] months with sorafenib and 5.6 [90% CI 2.8-6.0] months with placebo. There was no statistically significant difference (p=0.44).

6-month PFS rate was 42.5% [90% CI 30.0-54.4%] for patients in the sorafenib arm, and 35.1% [90% CI 23.9-46.5%] for patients in the placebo arm. Hazard Ratio was 0.84 [90% CI 0.58-1.22]. In the per-protocol set, median PFS was 6.1 months with sorafenib and 5.6 months with placebo (p=0.39).

Secondary endpoints:

Overall survival

In the full analysis set, 34 OS events were reported for the sorafenib arm, and 27 events for the placebo arm. Median OS was 9.6 [90% CI 7.3-14.0] months with sorafenib and 12.7 [90% CI 9.8-23.2] months with placebo (p=0.076). 12-month OS rate was 43.3% [90% CI 30.1-55.9%] with sorafenib and 52.8% [90% CI 39.4-64.5%] with placebo. Hazard Ratio was 1.57 [90% CI 1.03-2.41]. In the per protocol set, OS was 13.1 [90% CI 8.1-15.4] months with sorafenib and 13.8 [90% CI 10.2-23.3] months with placebo (p=0.22).

A statistically significant difference in OS was observed in the FAS for those patients receiving FOLFOX6 chemotherapy. With concomittant FOLFOX6, median OS in the sorafenib arm was 9.6 [90% CI 5.2-13.2] months, and 13.8 [90% CI 10.2-23.8] months in the placebo arm (p=0.026). With concomittant FOLFIRI, no significant difference was observed. Also, for patients with bevacizumab first line pre-treatment, median OS was significantly longer in the placebo group (14.9 months, 90% CI 10.2-n.a.) than with sorafenib (8.4 months, 90% CI 5.7-14.0, p=0.007), whereas there was a statistically nonsignificant trend towards longer OS in the sorafenib arm for patients without bevacizumab pre-treatment (13.1 vs. 7.4 months).

Response rate

In the sorafenib arm of the FAS, 10 patients (22.2%) achieved a partial response (PR), while 6 patients (11.5%) in the placebo arm achieved PR. Complete response (CR) was not documented. The difference was statistically not significant (p=0.11).

Disease control rate

Disease control rate was equal in both arms of the FAS: In the sorafenib arm, 25 patients (55.6%) achieved disease control, and 29 (55.8%) in the placebo arm.

Growth Modulation Index was not evaluated.

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Safety results:

The total number of cycles administered was 308 in the sorafenib arm (6.8 per patient) and 418 in the placebo arm (8.0 per patient).

Of the 45 patients treated in the sorafenib arm, 44 (97.8%) experienced at least one adverse event (AE), and 18 patients (40%) experienced at least one serious adverse event (SAE). Of the 52 patients in the placebo arm, all experienced an AE, with 15 patients (28.8%) thereof experiencing at least one SAE. See Table 1 for the number of patients who experienced a given SAE by CTCAE v3.0 class and term.

Few individual SAEs occurred in more than 2 patients per arm, i.e. at a frequency above 5%. Incidence of most individual SAEs seems balanced between treatment arms, with the exception of mucositis/stomatitis, which occurred in 3 patients (6.7%) in the sorafenib arm, but was not observed in the placebo arm. Many individual SAEs, though, were observed in one patient in the sorafenib arm and not at all in the placebo arm, eventually accounting for a markedly larger number of patients affected by SAEs in the sorafenib arm. This imbalance derives from several organ classes, including neurologic and cardiac events. Other events, including most serious gastrointestinal and constitutional symptoms and infections were balanced between treatment arms (see Table 1).

In the sorafenib arm, a total of 35 patients (77.8%) experienced at least one treatment-related AE. The rate was similar with placebo, where 37 patients (71.2%) were affected by treatment-related AEs as assessed by the investigator. For SAEs, the rates were equally balanced between treatment arms: With sorafenib, 7 patients (15.6%) had treatment-related SAEs, and likewise 7 patients (13.5%) in the placebo arm.

Conclusions

Efficacy: No statistically significant differences between the two treatment regimens were found for any endpoint. Especially for the primary endpoint PFS, both regimens were highly similar. Disease control rate showed a trend favoring the addition of sorafenib to the chemotherapy backbone. More markedly, data on overall survival in certrain patient subgroups indicate that sorafenib treatment might be detrimental in some situations, e.g. when combined with FOLFOX6 and in patients pre-treated with bevacizumab.

Safety: The observed adverse events are consistent with the known safety profiles of sorafenib and the backbone chemotherapy, as well as with the severity of the underlying disease. In the sorafenib arm, more patients experienced serious adverse events. This is most likely due to an additive effect of the study drug with the backbone chemotherapy.

Date of report: Final Version 2.0, 12 Oct 2020

Table 2: Frequency of patients with serious adverse events by CTCAE Category and CTCAE Term

	Sorafenib + CTx		Placebo + CTx	
	n	(%)	n	(%)
Number of patients	**45**	**(100.0%)**	**52**	**(100.0%)**
Patients with any event	**18**	**(40.0%)**	**15**	**(28.8%)**
Gastrointestinal - Any event	8	(17.8%)	10	(19.2%)
Diarrhea	3	(6.7%)	4	(7.7%)
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	2	(4.4%)	3	(5.8%)
Mucositis/stomatitis (clinical exam)	3	(6.7%)	0	(0%)
Anorexia	0	(0%)	2	(3.8%)
Nausea	1	(2.2%)	1	(1.9%)
Ascites (non-malignant)	1	(2.2%)	0	(0%)
Colitis	0	(0%)	1	(1.9%)
Dehydration	0	(0%)	1	(1.9%)
Enteritis	0	(0%)	1	(1.9%)
Esophagitis	1	(2.2%)	0	(0%)
Fistula, GI	0	(0%)	1	(1.9%)
Constitutional symptoms - Any event	4	(8.9%)	4	(7.7%)
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	2	(4.4%)	2	(3.8%)
Constitutional Symptoms - Other	3	(6.7%)	2	(3.8%)
Infection - Any event	4	(8.9%)	3	(5.8%)
Infection with unknown ANC	2	(4.4%)	2	(3.8%)
Infection with normal ANC or Grade 1 or 2 neutrophils	1	(2.2%)	0	(0%)
Infection - Other	1	(2.2%)	1	(1.9%)
Neurology - Any event	4	(8.9%)	0	(0%)
CNS cerebrovascular ischemia	1	(2.2%)	0	(0%)
Neuropathy: sensory	1	(2.2%)	0	(0%)
Psychosis (hallucinations/delusions)	1	(2.2%)	0	(0%)
Somnolence/depressed level of consciousness	1	(2.2%)	0	(0%)
Hepatobiliary/pancreas - Any event	2	(4.4%)	1	(1.9%)
Liver dysfunction/failure (clinical)	2	(4.4%)	0	(0%)
Hepatobiliary/Pancreas - Other	0	(0%)	1	(1.9%)
Cardiac arrhythmia - Any event	2	(4.4%)	0	(0%)
Supraventricular and nodal arrhythmia	2	(4.4%)	0	(0%)
Cardiac general - Any event	2	(4.4%)	0	(0%)
Hypertension	1	(2.2%)	0	(0%)
Cardiac General - Other	1	(2.2%)	0	(0%)
Metabolic/laboratory - Any event	2	(4.4%)	0	(0%)
Glucose, serum-low (hypoglycemia)	1	(2.2%)	0	(0%)
Metabolic/Laboratory - Other	1	(2.2%)	0	(0%)
Pain - Any event	2	(4.4%)	0	(0%)
Pain	2	(4.4%)	0	(0%)
Vascular - Any event	1	(2.2%)	1	(1.9%)
Thrombosis/thrombus/embolism	1	(2.2%)	1	(1.9%)
Dermatology/skin - Any event	1	(2.2%)	0	(0%)
Rash: hand-foot skin reaction	1	(2.2%)	0	(0%)
Renal/genitourinary - Any event	1	(2.2%)	0	(0%)
Cystitis	1	(2.2%)	0	(0%)
Secondary malignancy - Any event	0	(0%)	1	(1.9%)
Secondary malignancy - possibly related to cancer treatment	0	(0%)	1	(1.9%)

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