International Journal of Clinical Pharmacology and Therapeutics, Vol. 52 – No. 8/2014 (642-652)

ISSN 0946-1965

DOI 10.5414/CP202109
e-pub: May 7, 2014

FOLFIRI and sunitinib as first-line treatment in metastatic colorectal cancer patients with liver metastases – a CESAR phase II study including pharmacokinetic, biomarker, and imaging data

Klaus Mross[1], Max Scheulen[2], Dirk Strumberg[3], Jan Kuhlmann[4], Friederike Kanefendt[5], Fritz Sörgel[6], Ulrich Jaehde[5], Iris Burkholder[7], Berta Moritz[8], and Martin Büchert[9]

[1]Tumor Biology Center, Department of Medical Oncology, Freiburg, [2]Department Medical Oncology, University Hospital Essen, University Duisburg-Essen, Essen, [3]Department Hematology and Oncology, University Hospital Herne, University Bochum, Herne, [4]University Medical Center, Internal Medicine II, Freiburg, [5]Department of Clinical Pharmacy, Institute of Pharmacy, University Bonn, Bonn, [6]IBMP, Institute for Biomedical and Pharmaceutical Research, Nürnberg-Heroldsberg/Institute of Pharmacology, School of Medicine, University of Duisburg-Essen, Essen, [7]Department of Nursing and Health, University of Applied Sciences of the Saarland, Zweibrücken, Germany, [8]CESAR Central European Society of Anti-Cancer Research-EWIV, Vienna, Austria, and [9]Magnetic Resonance Development & Application Center (MRDAC) of the University Medical Center Freiburg, Freiburg, Germany

Key words
Phase-II study – metastatic colorectal cancer – cytotoxics – cytostatics – sunitinib

Trial registration:
NCT00806663

Received
December 31, 2013;
accepted
February 20, 2014

Correspondence to
Dr. Martin Büchert
Magnetic Resonance Development & Application Center (MRDAC) of the University Medical Center Freiburg,
Breisacherstraße 60a,
79106 Freiburg,
Germany
martin.buechert@uniklinik-freiburg.de

Abstract. Background: The aim of this study was the evaluation of pharmacokinetic parameters, biomarkers, clinical outcome, and imaging parameters in metastatic colorectal cancer (mCRC) patients treated with FOLFIRI plus sunitinib. Methods: mCRC patients with liver metastases were treated with FOLFIRI and sunitinib as 1st line therapy. At protocol-defined time points, multicontrast magnetic resonance imaging (MRI) measurements, computed tomography (CT) scans, pharmacokinetics (PK), and biomarker analyses were performed during the first and second treatment cycle. Thereafter, patients were treated until tumor progression, investigator's decision due to toxicity, or patient withdrawal. Results: 28 patients were screened, 26 were included, and 23 received at least one study medication. Full safety analysis was performed in 23 patients. Full PK and biomarker analyses were performed in 21 patients. Strong responses in tumor size reduction forced a change from the original imaging timing scheme. This unforeseen change in the timing scheme resulted in subgroups too small for meaningful statistical analysis of most imaging parameters. Thus, only a descriptive analysis of the MRI data was possible. In 21/22 patients, MRI showed a decrease of the liver metastases. Best response was partial remission (PR) in 8/17 patients. Plasma concentrations of sVEGFR-2 and sVEGFR-3 decreased in all patients. The majority of the patients developed some kind of toxicity not always deducible to FOLFIRI or sunitinib. Conclusions: Due to the observed side effect profile, FOLFIRI plus sunitinib 37.5 mg per day cannot be recommended for previously untreated mCRC.

Introduction

Blood vessel evolution is necessary for each tumor development [1]. Angiogenesis is a factor that is important in metastatic colon cancer. Different anti-angiogenic drugs are now approved for different situations (first line, second line, and last line) [2, 3, 4]. Since it is known that the VEGF/VEGFR system plays a critical role in angiogenesis, inhibitors either acting directly at VEGF or at its receptors intra- and extracellularly were developed. Mostly drugs bind to the receptors and prevent the functional activity of VEGF [1]. The inhibition of the angiogenesis as therapeutic mechanism of action was initialized with bevacizumab in combination with FOLFOX or FOLFIRI in metastatic colorectal cancer (mCRC) patients in

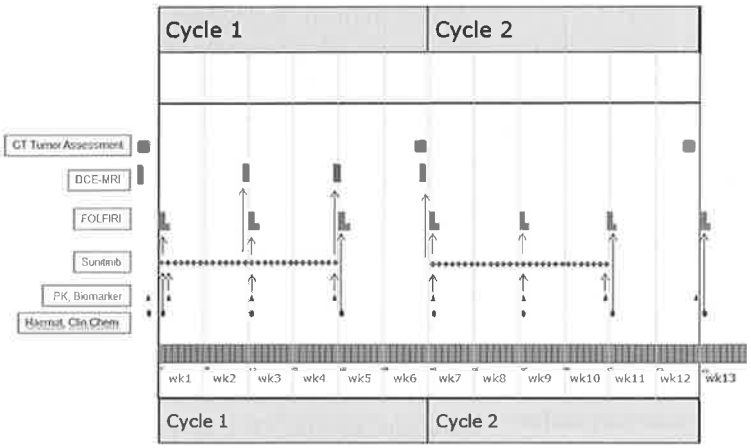

Figure 1. Time lines for PK, biomarker, treatment, multi-contrast MRI and DCE-USI, and efficacy analyses. The study time lines of the first two cycles are shown.

first line [5]. As bevacizumab primarily acts as a VEGF-A trap, it is obvious to try other drugs that interfere with the VEGF-VEGFR system. Another strategy is the inhibition of tyrosine kinases involved in the angiogenesis, such as the VEGFR family. The observed overexpression of proangiogenic factors and their receptors as well as the efficacy of the anti-angiogenic therapy with bevacizumab in patients with mCRC was the rational for this study. Furthermore, first results of a phase I study were published showing that mCRC patients can be treated efficiently and with acceptable toxicity by FOLFIRI in combination with sunitinib at 37.5 mg (instead of 50 mg) in a 4-weeks-on and 2-weeks-off treatment schedule [3]. Sunitinib is a multikinase inhibitor interfering with the VEGFR system and other kinases [12]. In tumor biopsies from patients undergoing sunitinib treatment, it was shown that intratumoral concentrations in the order of 10 µmol/L were 30-fold higher than plasma concentrations [7]. To get more insights into the complex relationships between imaging markers, biomarkers, and the pharmacokinetics in patients with mCRC, we started an investigator-initiated multicenter phase II trial (IIT) in 2008. A translational research program including pharmacokinetic (sunitinib and SU12662) and biomarker (sVEGFR-2 and -3) measurements was included [8]. In addition to imaging evaluation derived from multi-contrast magnetic resonance imaging (MRI), secondary parameters like objective response rate after cycle 1, after cycle 2, best overall response and toxicity were documented (Figure 1).

Materials and methods

Study design and treatment

This multicenter, open label, phase II study employed a statistical design that was intended to test multi-contrast MRI parameters and their reduction regarding the two statistical hypotheses that: there would be no change after 12 weeks, or there would be a reduction after 12 weeks. With 20 evaluable patients for all variables considered, a one-sided paired t-test has a power of at least 63% when testing at the level of 0.05. Based on this and accounting for 10% non-evaluable cases, the study planned to recruit 22 patients in four participating centers. The study medication consisted of folinate, fluorouracil, and irinotecan (FOLFIRI) in combination with 37.5 mg sunitinib daily. FOLFIRI was given in the conventional 2-weeks schedule (q2w), whereas sunitinib was administered once per day in a 4-weeks-on and 2-weeks-off treatment schedule (4/2 schedule) [6]. Six weeks were defined as one therapy cycle.

Patients

Included in this trial were patients aged 18 years and older, with metastatic, inoperable, and histologically confirmed adenocarcinoma of the colon; liver metastasis of at least 2 cm, and a measurable disease using Response Evaluation Criteria In Solid Tumors (RECIST) 1.0 criteria [9] as well as an ECOG (Eastern Cooperative Oncology Group) performance status 0 or 1; adequate liver and hematological function. Exclusion criteria included a prior chemotherapy for metastatic disease, surgery or radiotherapy within 4 weeks of starting study drug treatment, known brain metastasis, myocardial infarction, congestive heart failure, uncontrolled hypertension, and bleeding. The study received positive ethical votes from all participating centers and BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) approval. It was conducted in accordance with Good Clinical Practice guidelines. Written informed consent was mandatory.

Imaging

According to the study protocol, MRI scans were to be performed at baseline, 4, 10, and 12 weeks after start of treatment. Only patients with liver metastases larger than 2 cm in diameter were included. During the analysis of the first 4 patients, it was recognized that the target lesion in the liver for Dynamic Contrast Enhanced MRI (DCE-MRI) rapidly became too small for accurate DCE-MRI measurements in responding patients. The protocol was amended to gather these imaging parameters earlier (baseline, 2, 4, and 6 weeks) than in the original plan. This was done to ensure that target lesions did not become too small for meaningful assessment with DCE-MRI during follow-up or even become immeasurable.

In addition to anatomical MRI this included DCE-MRI and diffusion weighted MRI (DW-MRI). Data acquisition was performed on a clinical 1.5T system (Magnetom Symphony; Siemens, Erlangen, Germany). Details can be found in [10, 11]. The primary MRI parameters determined were the baseline value of longitudinal relaxation rate (R10), initial area under the concentration curve for first the 60 seconds (iAUC60), transfer constant (Ktrans), and the ratio extravascular extracellular volume/tissue volume (ve) based on DCE-MRI. Additionally, apparent diffusion coefficient (ADC) was calculated based on DW-MRI. The changes of this parameter under therapy were investigated. Regarding the imaging parameters, this temporal evolution was of main interest. Parameters were analyzed in a region of interest (ROI) placed in the target lesion using a supervised semi-automatic procedure.

In an additional analysis, this ROI was split into two additional ROIs representing the core (CORE) and the rim (RIM) part of the target lesion, since the composition of lesions is often heterogenic. Separate analyses of both ROIs were carried out. MRI data were grouped by their status at week 6. The four classes were stable disease SD, stable disease partial response not confirmed SD(NC), partial response PR, and progressive disease PD.

Tumor response and toxicity

For the RECIST tumor response evaluation, computed tomography (CT) scans were performed at baseline, after 6 weeks (= 1 cycle), after 12 weeks (= 2 cycles), and thereafter at the discretion of the physician, but at least every 2 cycles or in case of suspicious progressive disease. Separate RECIST analysis was carried out using the anatomical MRI data, which were acquired during the MRI examinations. MRI was limited to the liver area. Resulting CT-based and MRI-based values were compared.

Toxicity according to the common terminology criteria for adverse events (CTCAE) catalogue version 3.0 [12] was graded. The patient's individual time to treatment stop due to progression, toxicity, or patient's demand was recorded.

Pharmacokinetics and biomarker response

Plasma samples for pharmacokinetic and biomarker analyses were collected during the first two cycles. The time plan for all samples is shown in Figure 1. Plasma concentrations of sunitinib and SU12662 were measured using a validated High Performance Liquid Chromatography – Mass Spectrometry/Mass Spectrometry (HPLC-MS/MS) method [13]. Soluble VEGFR-2 was determined by commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA). Soluble VEGFR-3 was measured using a validated ELISA, previously described in detail [8]. The concentration-time courses of the active drug and all biomarkers were analyzed descriptively. Biomarker response to sunitinib administration was assessed as change from the corresponding baseline level [14, 15].

A systematic correlation analysis was performed to identify possible relationships between the imaging parameters and pharmacokinetic parameters of sunitinib and SU12662 using R® (The R Foundation for Statistical Computing, version, 2.10.1, 2009). A p-value of 0.05 was defined as statistically significant.

Results

While only preliminary results of using limited available data, were published in

assessment interval	1	2	3	4	5	7	8	11	Best overall
Pat_ID	Response	Response	Response	Response	Response	Response	Response	Response	Response
01_01	SD(NC)	PR	SD			PD			PR
01_02	SD(NC)	PR	PD						PR
01_04	SD	SD	SD						SD
01_05	SD(NC)	PR		PD					PR
02_01	SD	SD	SD	SD	SD	PD			SD
02_02	SD	SD	SD						SD
02_03	SD	SD	SD	PD					SD
02_04	SD	SD	PR						PR
03_01	SD	SD	PD						SD
03_02		SD	SD	SD					SD
03_03		SD		SD					SD
04_01	SD	SD	SD		PD				SD
04_03	SD	SD	PR		PR	PD			PR
04_04	SD	SD(NC)	PR						PR
04_06	SD	SD(NC)		PR	PR	PR	PR	PR	PR
04_07	SD	SD		PD					SD
04_09	SD	SD(NC)	PR		PD				PR

Figure 2. Individual response assessment over time (cycle) and best overall response. Only patients who were at least 8 weeks in therapy are shown. SD = stable disease; NC = not confirmed; PR = partial response; PD = progressive disease. The last column lists the "Best overall response under therapy".

2011 in a conference abstract [16], here the data analysis of all patients is presented.

Patients

28 patients were recruited. Five patients never received any study medication (screening failure (n = 2), consent withdrawn (n = 2), investigator's decision prior to study start (n = 1)). Therefore, 23 patients were evaluable for safety. Median time in treatment (calculated from first intake to last intake of study medication) was 18.4 weeks (range: 2.3 – 50.7 weeks). 18 patients completed one [2, 3, 6, 7, 12] treatment cycle, and 16 patients completed two [3; 4; 5; 6; 7] cycles. Treatment was stopped due to disease progression in 10 patients and due to an adverse event in 8 patients. In two patients, liver lesions decreased thus far that partial liver resection was performed. Other reasons for end of treatment were losts to follow-up (1 patient), withdrawal of informed consent (1 patient), or investigator's decision (1 patient).

Tumor response

Out of 23 patients, 17 patients received study therapy for more than 8 weeks. They were subsequently evaluated for response, and the complete staging CT scans, including thorax/abdomen with RECIST evaluation, was performed. After one treatment cycle, the SD rate was 12/17 (70%), the SD(NC) rate

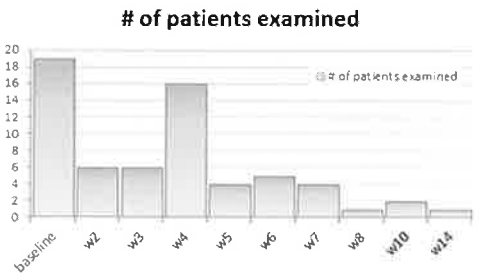

Figure 3. Number of patients examined with multi-contrast MRI as a function of time. The pattern results from the change of the timing scheme after the first 4 patients.

3/17 (18%), and 2/17 (12%) patients were not evaluated in this cycle. After two cycles, the PR and combined SD & SD(NC) rate was 3/17 (18%) and 14/17 (82%), respectively. PR 8/17 (47%) and SD 9/17 (53%) were the best overall response in the study. Individual response over time and best overall response for patients who were at least 8 weeks in therapy are summarized in Figure 2.

Imaging

Baseline multi-contrast MRI data were acquired in 25 patients. RECIST evaluation based on MRI data with at least baseline and week 2 measurements were done in 22 patients. For 19 patients, at least two valid DCE-MRI measurements, including a valid baseline scan, were analyzed. For the first 4 patients, MRI examinations showed such a strong response regarding tumor size within the first cycle that the resulting lesion size was below the limit necessary for reliable DCE-MRI examinations. Due to these unexpected, strong responses, the original timing scheme for MRI examinations had to be adapted to a shorter overall time frame, as described in the methods section.

Due to this alteration in the timing scheme, the originally planned group analysis at baseline, 4, 10, and 12 weeks after start of treatment became inappropriate. This led to different group populations at the various time points, which finally were: ((baseline/19), (week 2/6), (week 3/6), (week 4/16), (week 5/4), (week 6/5), (week 7/4), (week 8/1), (week 10/2), and (week 14/1)) (time point/# of patients) as shown in Figure 3. In combination with individual patient participation durations, this resulted in the

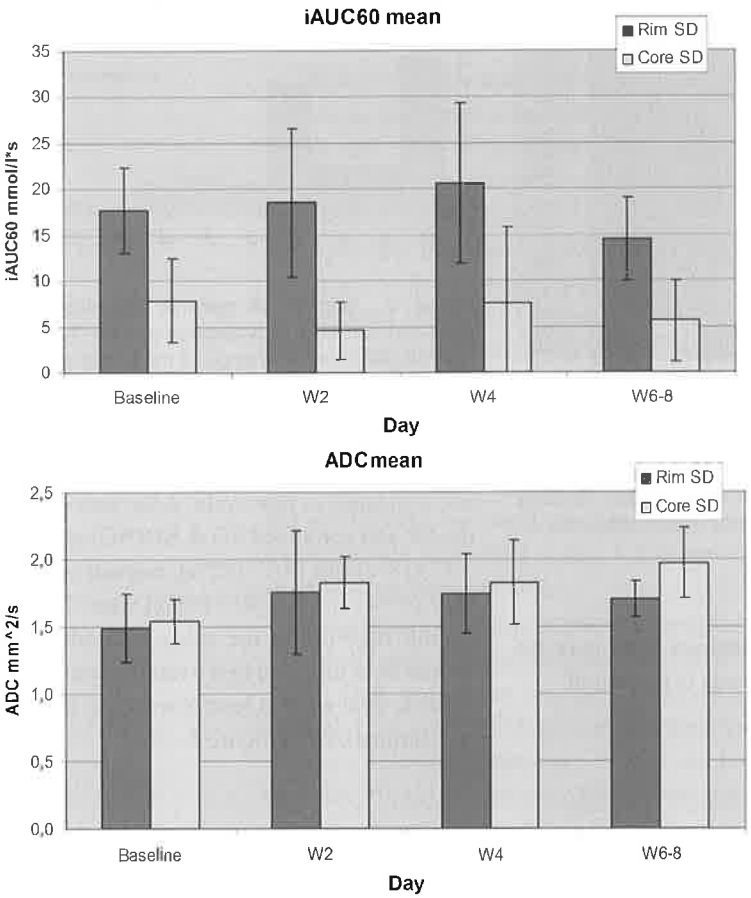

Figure 4. MRI parameter comparison. Comparison of mean iAUC60 and ADC values over the various time points for lesion rim and lesion core. While there are larger differences between rim and core for iAUC60, the ADC values show only minor differences.

following number of patients as a function of performed MRI examinations, which finally were: ((2/4), (3/8), (4/6), (5/1)) (# of examinations/# of patients).

Averaged over all MR measurements for each time point and each calculated DCE parameter, the difference between RIM and CORE ROIs were larger than 18% with a range of 18% (R10 at week 2) to 58% (Ve at baseline). This difference between RIM and CORE of the target lesion is already seen on the individual patient level, reflecting a more active lesion rim compared to the core. Looking at the ADC differences between RIM and CORE and their average for each time point of all patients, each difference was below 10%. Given the standard deviation, this was not a significant difference.

The mean difference of iAUC60 and ADC showed only small variability over time, as plotted in Figure 4.

Within accuracy of the resulting small patient subgroups, for none of the multi-contrast MRI parameters a significant change over time could be detected.

However, single patients showed similar changes like the patient example in Figure 5, including anatomical MRI, lesion size measures, and time courses from DCE-MRI. The concentration-time courses of the DCE-MRI contrast agent in the bottom left show strong reduction at follow-up examinations compared to baseline. This is also reflected in the initially decreasing course of iAUC60 over time (bottom right) and goes along with a reduction in lesion size (top right). ADC values increase by ~ 40% compared to baseline (bottom right).

In addition to RECIST analysis based on CT data for 22 patients, the sum of the lesion sizes in the liver were calculated by MRI, which reflect only the anti-cancer efficacy in the liver. In this MRI evaluation of the liver, the majority (21/22) of patients showed an initial decrease (Figure 6).

The comparison of RECIST data based on CT and MRI as displayed in Figure 7 shows a good correlation of 0.81 although their acquisition dates differ by a few days, and compared to CT, the MRI examination volume was limited to the liver area.

Pharmacokinetic and biomarker analysis

In patients receiving 37.5 mg of sunitinib, median plasma trough concentrations of 39.4 ng/mL (interquartile range (IQR): 19.6 – 53.3 ng/mL) for the parent drug and 17.5 ng/mL (8.1 – 27.5 ng/mL) for its metabolite SU12662 were observed after 14 days (Figure 8).

Median baseline concentrations of 9,362 pg/mL (IQR: 7,898 – 9,941 pg/mL) and 17,501 pg/mL (IQR: 14,617 – 30,632 pg/mL) were observed for sVEGFR-2 and sVEGFR-3, respectively. Plasma concentrations of both soluble receptors decreased after sunitinib intake, qualifying sVEGFR-2 and sVEGFR-3 as pharmacodynamic markers of sunitinib treatment. After 28 days of treatment, plasma concentrations of sVEGFR-2 decreased to 61% (IQR: 57 – 72%) (Figure 9a) and plasma concentrations of sVEGFR-3

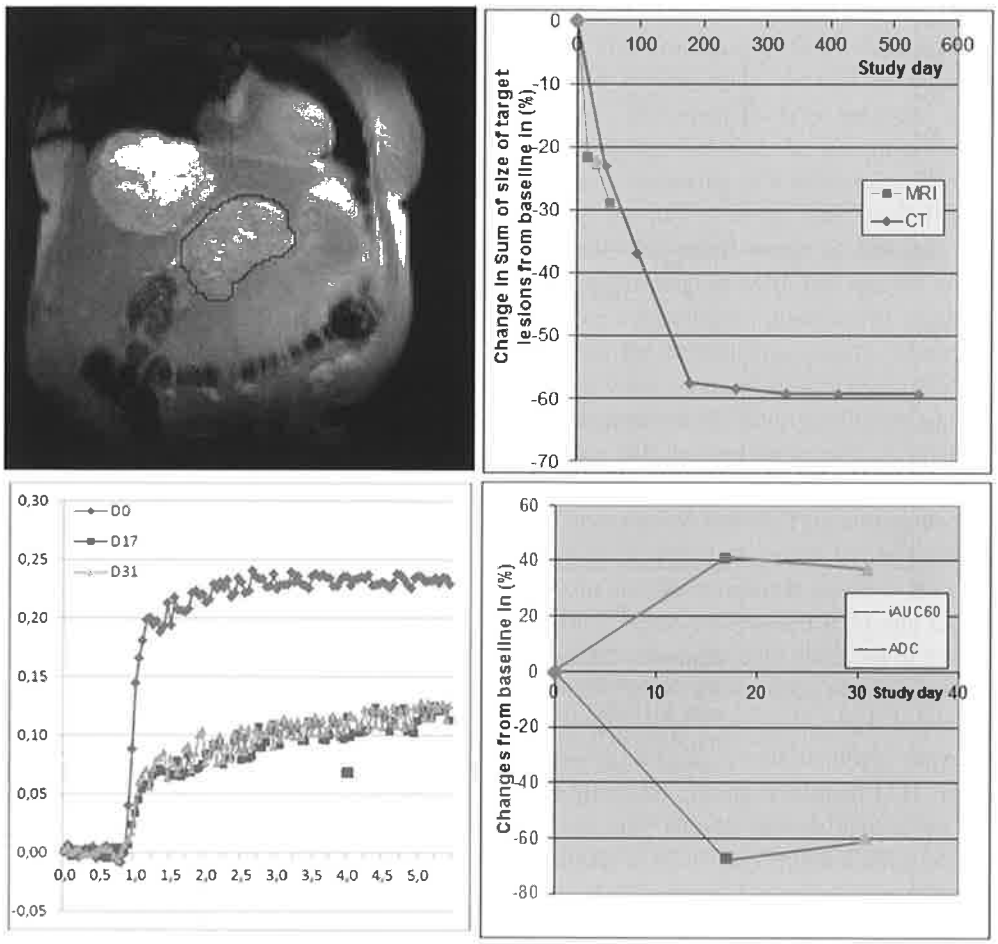

Figure 5. Single case example: Patient 0406. MRI with drawn region of interest of target lesion in the liver. Below are the contrast agent concentration time curves of the three examinations. The plots on the right show a strong decrease of the perfusion dominated parameter iAUC60, an increase in ADC (bottom) accompanied with a tumor size (top) reduction over the study time curse. Due to patient-related reasons, functional MRI of day 52 could not be acquired.

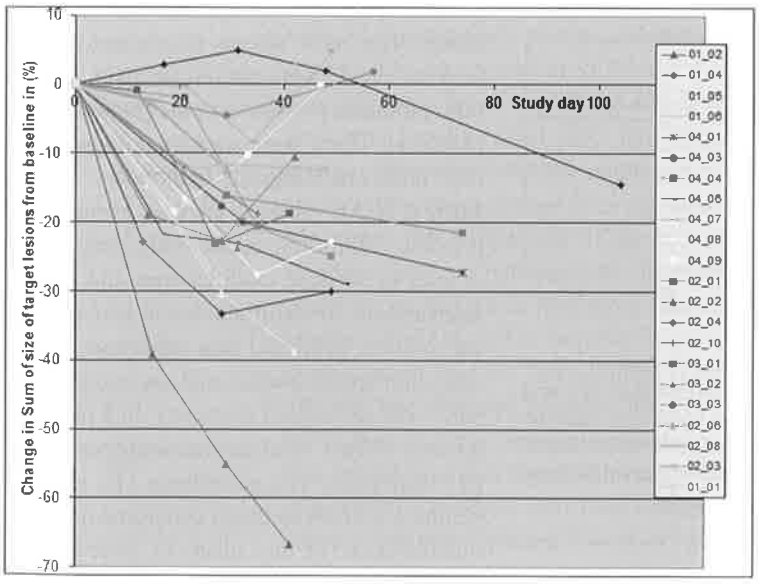

Figure 6. Analysis of the individual target lesions sizes over the study course. Data do not necessarily reflect the efficacy of the treatment on all present lesions.

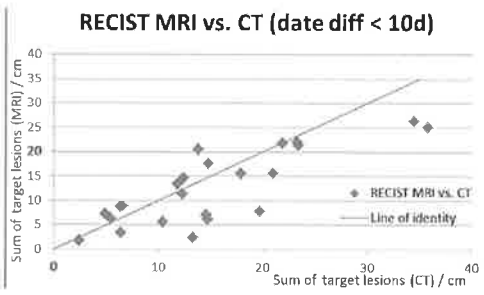

Figure 7. Lesion sizes. Sum of target lesion sizes evaluated with MRI and CT data. Only data sets whose date of acquisition differ by less than 10 days were included.

to 58% (IQR: 47 – 80%) (Figure 9b) of the corresponding baseline level. After the end of therapy biomarker levels increased again up to concentrations near baseline. Concentration-time profiles did not differ among the study centers for either soluble receptor. This phenomenon seems therefore reliable

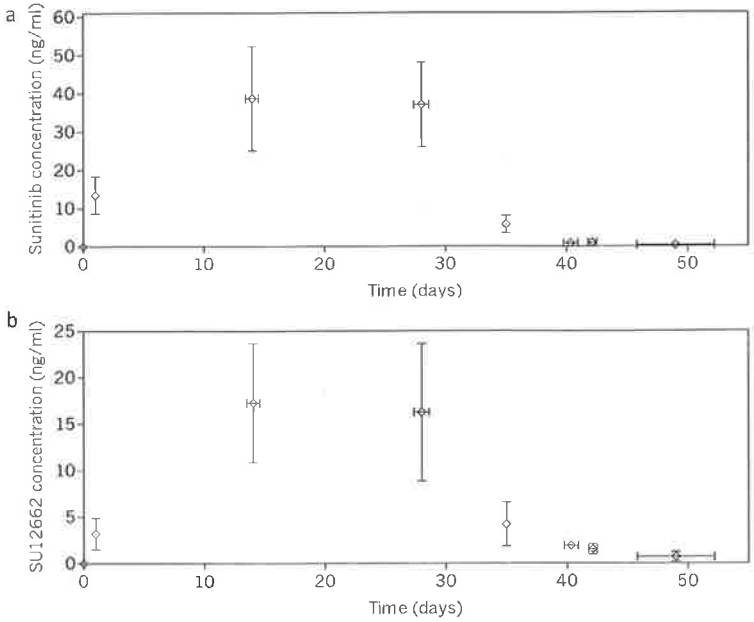

Figure 8. Concentration-time profiles I. Concentration-time profile of sunitinib (a) and its active metabolite SU12662 (b) following administration of 37.5 mg sunitinib (↑) in patients with metastatic colorectal cancer (mean ± SD, n = 21) in the first therapy cycle.

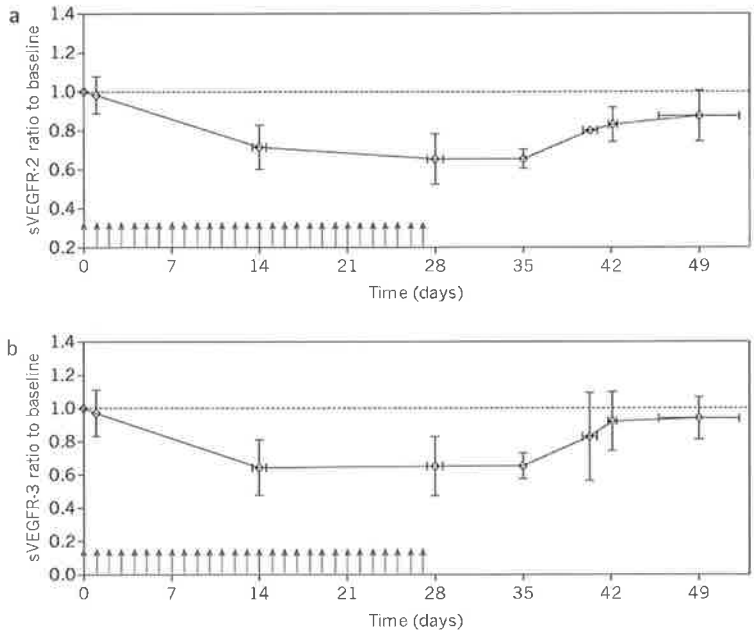

Figure 9. Concentration-time profiles II. Concentration-time profiles of sVEGFR-2 (a) and sVEGFR-3 (b) as ratio to their respective baseline level (mean ± SD, n = 21) for all patients with metastatic colorectal cancer after application of 37.5 mg sunitinib (↑) in the first therapy cycle.

and shows that these systems are rapidly responding systems and interruptions or drug free holidays should be avoided if possible. Correlation analyses between individual imaging and pharmacokinetic parameters of sunitinib and SU12662 did not reveal any relationship.

Table 1. Adverse events.

Adverse events	No of patients (%)
Hematological adverse events	
Neutropenia	10 (44%)
Leukopenia	7 (31%)
Anemia	2 (9%)
Thrombocytopenia	2 (9%)
Non-hematological adverse events	
Abdominal pain	2 (9%)
Stomatitis	3 (13%)
Pulmonary embolism	3 (13%)
Hypertension	2 (9%)
Adverse events of special interest	
Hyperkeratosis	1 (4%)
Mucosal inflammation	1 (4%)
Infected skin ulcer	1 (4%)

Grade ≥ 3 adverse events reported in > 5% of patients and adverse events of special clinical interest, regardless of causality.

Adverse events and toxicity

The toxicity was remarkable and treatment delays, interruptions, or reductions were necessary to manage the toxicity. Severe (grade ≥ 3, CTCAE 3.0) neutropenia occurred in 10/23 (43%) and leukopenia in 7/23 (30%) patients at least once during the treatment phase. The most severe non-hematological adverse events were abdominal pain, stomatitis, pulmonary embolism, and hypertension (Table 1). There were six hematological and one non-hematological (pulmonary embolism) CTCAE grade 4 adverse events with possible relationship to the study medication. A total of 36 dose modifications and 8 dose interruptions for sunitinib due to hematological toxicity, hand and foot syndrome, infection, diarrhea, stomatitis, melena, and anal fissure were considered necessary. In 8 patients, adverse events (leukopenia/neutropenia (2), polyneuropathy (1), paresthesia (1), palmar-plantar erythrodysesthesia syndrome/mucosal inflammation (1), anal ulcer (1), infected skin ulcer (1), general physical health deterioration (1)) led to discontinuation of treatment with sunitinib.

Discussion

In this multicenter investigator initiated trial, 23 patients with mCRC were treated with FOLFIRI in combination with sunitinib. Imaging parameters as well as the pharmacokinetics of sunitinib and its active metabolite SU12662 and appropriate biomarkers were investigated in this population. Specific challenges were the logistics and the implementation of the complete translational research program in four study centers as well as the unexpected, strong response, which forced a timing change in the imaging acquisition scheme.

The treatment was similar to the one published by Starling et al. [6], whereas the definition of a cycle and the kind and frequency of measured parameters was different from that study. In addition to safety aspects, an extended number of parameter determinations were included in the study. Median dose normalized trough concentrations (C_{trough}/D) of sunitinib and SU12662 were slightly higher compared to data previously published for cancer patients treated with 50 mg sunitinib [17]. Sunitinib is mainly metabolized via CYP3A4, and differences in liver function could, therefore, explain these differences as well as the observed variability among the mCRC patients in our study. Decreasing concentrations of sVEGFR-2 and sVEGFR-3 after sunitinib administration correspond to results previously published for patients with different cancer types [18]. In mCRC patients treated with 50 mg sunitinib, plasma concentrations of sVEGFR-2 decreased to 45.2% and plasma concentrations for sVEGFR-3 to 40.5% of the respective baseline level [19]. This indicates a larger biomarker response compared to our study with a lower dose of 37.5 mg sunitinib. Moreover, the comparison of the biomarker response between patients with different tumor entities treated at the same dose level suggests that biomarker response is not only dependent on dose but also on tumor type [16, 18, 20]. The observed temporal link between biomarker response and sunitinib administration, which was also observed in healthy volunteers [21], confirms that both proteins are reliable pharmacodynamic markers for the anti-angiogenic activity of sunitinib.

In a recently published study, Ktrans and iAUC 90 as well as iAUC120 were identified as predictors of the tumor response [22] in patients treated with FOLFIRI in combination with bevacizumab. Multi-contrast MRI as used in this study showed no clear-cut pattern. The analysis was strongly influenced by the fact that the aim of complete data sets consisting of 4 MRI measurements during the first 6 weeks was missed in all patients. The small group of subjects with valid multi-contrast MRI data sets did not allow for a meaningful quantitative subgroup analysis for certain time points. Therefore, results were reported descriptively. Except for the apparent diffusion coefficient (ADC), all other MR derived parameters showed differences between the RIM and the CORE of the investigated lesion. This corresponds to the known image of active tumor tissue in the rim and more necrotic tissue in the core. Those differences between RIM and CORE for ADC values are only observed to a much smaller extent. They could be explained by the counteracting increasing and decreasing diffusion effects of cell swelling, necrosis, and apoptosis during treatment [23]. These effects may largely cancel themselves out, resulting in no or only minor changes of the mean ADC values. No correlation to tumor response, progression free survival, or time to end of study treatment was observed.

Although the study was unable to acquire sufficient imaging data for statistically meaningful subgroup analysis, single patient data sets show interesting behavior of imaging parameters over the study course as shown in Figure 5. This patient showed stable disease within the first 14 weeks of treatment followed by a partial response until the end of the study (week 77). This response pattern corresponds to the imaging findings of a strong reduction in lesion size as well as in perfusion related parameters like iAUC60. The observed increase in ADC could be explained by an increasing part of necrotic tissue in the lesion during therapy.

The clinical efficacy was high, with an absence of progression in nearly all patients during the first (6 weeks) and second cycle (12 weeks). The anti-cancer therapy had a rapid onset of action, and further tumor reduction was observed after the second and following cycles (initially after one cycle 5 partial remissions, climbing up as best response to 8 partial remissions). The time to unacceptable toxicity differed markedly be-

tween patients. Nevertheless, these results are similar to those for patients treated with FOLFOX or FOLFIRI and bevacizumab as 1st line therapy [24]. In general, bevacizumab seems to exhibit a better side effect profile than sunitinib in combination with FOLFIRI. The toxicity of the drug combination FOLFIRI + sunitinib exceeded the initial expectations based on [5]. Meanwhile, also a phase III study was stopped after inclusion of 768 patients due to toxicity and lack of advantage in anti-tumor efficacy [25]. These unforeseen results affected the conduction of this phase II trial, which was stopped soon thereafter. Toxicity seen in this study was also considerable, although nausea and vomiting grade ≥ 3, prominent toxicities in the phase III study, were not observed in our study, which might have been due to the stricter anti-emetic regimen used in our clinical study. In addition, several cases of fatigue grade 2 were reported in our study, but no grade 3 fatigue. Hematological toxicities, hypertension, thrombotic events, and stomatitis were found in comparable rates in both studies. Since most of the side effects could be initiated by both administered drugs as well as by many other substances, a clear assignment to FOLFIRI or sunitinib alone cannot be made based on our study.

The addition of a tyrosine kinase inhibitor to either FOLFOX or FOLFIRI for the treatment of mCRC patients does not seem to be beneficial as some prominent drugs like vatalanib, sunitinib, and cediranib failed in similar situations [25, 26, 27]. Up to now, bevacizumab remains the only approved anti-angiogenic agent used as 1st line treatment in metastatic colon cancer patients. Meanwhile, bevacizumab has also been approved for second-line therapy, which can be summarized under the catchphrase "bevacizumab beyond progression" [2]. The same holds for aflibercept, which is approved for a second-line therapy [3, 8]. The triple angiokinase inhibitor BIBF1120 had shown some interesting activity/toxicity profile when compared with bevacizumab directly in a randomized first-line study [28]. BAY 73-4506 (Regorafenib) has shown a small survival advantage prospectively investigated against best supportive care. Perhaps BIBF1120 has the ability as potential competitor in this indication because BIBF1120 is the first oral TKI that has less side effects than bevacizumab while efficacy seems to be comparable [29, 30]. Regorafenib, a multi-TKI, is already approved for the treatment of mCRC patients as last-line therapy [4]. However, it is obvious from clinical experience and reported in literature that regorafenib is more toxic than bevacizumab [1, 2, 4]. An oral anti-angiogenic drug without severe toxicity problems would be highly welcome.

Conclusion

The combination FOLFIRI plus sunitinib is more toxic than what is known from FOLFIRI or FOLFIRI plus bevacizumab. The cancer control rate is high, but the objective response rate of the combination does not exceed those rates for FOLFIRI alone. Parameters derived from multi-contrast MRI could only show changes on an individual patient level. The soluble VEGF receptors 2 and 3 reflect the pharmacodynamic activity of sunitinib. The clinical efficacy is high, with an absence of progression in nearly all patients during the first (6 weeks) and second cycle (12 weeks). The anti-ancer therapy had a rapid onset of action, and further tumor reduction was observed after the second and following cycles. Due to the toxicity of the combination therapy, treatment modifications and interruptions were frequent, and in 8 out of 23 patients, treatments were ended prematurely due to an adverse event. The findings of this study are consistent with previous observations [6, 25]. FOLFIRI plus 37.5 mg daily sunitinib is not recommended for previously untreated mCRC. A less toxic oral anti-angiogenic drug is needed as a new therapeutic option for such cancer patients.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgments

The trial was sponsored by an IIT grant to K.M. from Pfizer Pharma GmbH. The trial was organized and coordinated by COO (CESAR's Central Office, Vienna, Austria).

References

[1] *Mross K, et al.* Angiogeneseinhibition in der Onkologie. Bremen: UNI-MED Verlag AG; 2007.

[2] *Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, von Moos R, Viéitez JM, Bouché O, Borg C, Steffens CC, Alonso-Orduña V, Schlichting C, Reyes-Rivera I, Bendahmane B, André T, Kubicka S; ML18147 Study Investigators.* Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013; *14:* 29-37.

[3] *Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegra C.* Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012; *30:* 3499-3506.

[4] *Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group.* Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; *381:* 303-312.

[5] *Starling, N. et al.* Phase I Study to Evaluate the Safety and Efficacy of Sunitinib in Combination with FOLFIRI in Treatment-naive Metastatic Colorectal Cancer (mCRC). J Clin Oncol Meet Abstr. 2008; *26:* no. 15_suppl 3563.

[6] *Starling N, Vázquez-Mazón F, Cunningham D, Chau I, Tabernero J, Ramos FJ, Iveson TJ, Saunders MP, Aranda E, Countouriotis AM, Ruiz-Garcia A, Wei G, Tursi JM, Guillen-Ponce C, Carrato A.* A phase 1 study of sunitinib in combination with FOLFIRI in patients with untreated metastatic colorectal cancer. Ann Oncol. 2012; *23:* 119-127.

[7] *Gotink KJ, Broxterman HJ, Labots M, de Haas RR, Dekker H, Honeywell RJ, Rudek MA, Beerepoot LV, Musters RJ, Jansen G, Griffioen AW, Assaraf YG, Pili R, Peters GJ, Verheul HM.* Lysosomal sequestration of sunitinib: a novel mechanism of drug resistance. [Erratum appears in Clin Cancer Res. 2012 Jan 1;18(1):318]. Clin Cancer Res. 2011; *17:* 7337-7346.

[8] *Kanefendt F, Lindauer A, Mross K, Fuhr U, Jaehde U.* Determination of soluble vascular endothelial growth factor receptor 3 (sVEGFR-3) in plasma as pharmacodynamic biomarker. J Pharm Biomed Anal. 2012; *70:* 485-491.

[9] *Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; *92:* 205-216.

[10] *Mross K, et al.* Safety, phamacokinetics and pharmacodynamic (DCE-MRI) in patients with metastatic colorectal cancer treated in a phase I study with BIBF 1120, the first triple angikinase inhibitor. In AACR-NCI-EORTC Conf. (Philadelphia (poster), 2005).

[11] *Fasol U, Frost A, Büchert M, Arends J, Fiedler U, Scharr D, Scheuenpflug J, Mross K.* Vascular and pharmacokinetic effects of EndoTAG-1 in patients with advanced cancer and liver metastasis. Ann Oncol. 2012; *23:* 1030-1036.

[12] *Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN, Rubin P.* CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003; *13:* 176-181.

[13] *Rodamer M, Elsinghorst PW, Kinzig M, Gütschow M, Sörgel F.* Development and validation of a liquid chromatography/tandem mass spectrometry procedure for the quantification of sunitinib (SU11248) and its active metabolite, N-desethyl sunitinib (SU12662), in human plasma: application to an explorative study. J Chromatogr B Analyt Technol Biomed Life Sci. 2011; *879:* 695-706.

[14] *Kanefendt F, et al.* Pharmacokinetic/Pharmacodynamic Modeling of Biomarker Response to Sunitinib in Patients with Metastatic Colorectal Cancer. In 12th Int. Congr. Ther. Drug Monit. Clin. Toxicol. 2011 264 (Stuttgart, 2011).

[15] *Kanefendt F, Lindauer A, Kinzig M, Strumberg D, Scheulen ME, Mross K, Fischer R, Moritz B, Sörgel F, Jaehde U.* Biomarker response on exposure to sunitinib and its primary metabolite (SU12662) in metastatic colorectal cancer patients. Int J Clin Pharmacol Ther. 2011; *49:* 88-90.

[16] *Mross K, Büchert M, Fasol U, Jaehde U, Kanefendt F, Strumberg D, Arends J, Hense J, Moritz B, Fischer R, Scheulen ME.* A preliminary report of a Phase II study of folinic acid, 5-fluorouracil, irinotecan (FOLFIRI) plus sunitinib with toxicity, efficacy, pharmacokinetics, biomarker, imaging data in patients with colorectal cancer with liver metastases as 1st line treatment. Int J Clin Pharmacol Ther. 2011; *49:* 96-98.

[17] *Faivre S, Delbaldo C, Vera K, Robert C, Lozahic S, Lassau N, Bello C, Deprimo S, Brega N, Massimini G, Armand JP, Scigalla P, Raymond E.* Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol. 2006; *24:* 25-35.

[18] *Deprimo SE, Bello CL, Smeraglia J, Baum CM, Spinella D, Rini BI, Michaelson MD, Motzer RJ.* Circulating protein biomarkers of pharmacodynamic activity of sunitinib in patients with metastatic renal cell carcinoma: modulation of VEGF and VEGF-related proteins. J Transl Med. 2007; *5:* 32.

[19] *Saltz LB, Rosen LS, Marshall JL, Belt RJ, Hurwitz HI, Eckhardt SG, Bergsland EK, Haller DG, Lockhart AC, Rocha Lima CM, Huang X, DePrimo SE, Chow-Maneval E, Chao RC, Lenz HJ.* Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. J Clin Oncol. 2007; *25:* 4793-4799.

[20] *Burstein HJ, Elias AD, Rugo HS, Cobleigh MA, Wolff AC, Eisenberg PD, Lehman M, Adams BJ, Bello CL, DePrimo SE, Baum CM, Miller KD.* Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with

metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2008; *26:* 1810-1816.

[21] *Lindauer A, Di Gion P, Kanefendt F, Tomalik-Scharte D, Kinzig M, Rodamer M, Dodos F, Sörgel F, Fuhr U, Jaehde U.* Pharmacokinetic/pharmacodynamic modeling of biomarker response to sunitinib in healthy volunteers. Clin Pharmacol Ther. 2010; *87:* 601-608.

[22] *Hirashima Y, Yamada Y, Tateishi U, Kato K, Miyake M, Horita Y, Akiyoshi K, Takashima A, Okita N, Takahari D, Nakajima T, Hamaguchi T, Shimada Y, Shirao K.* Pharmacokinetic parameters from 3-Tesla DCE-MRI as surrogate biomarkers of antitumor effects of bevacizumab plus FOLFIRI in colorectal cancer with liver metastasis. Int J Cancer. 2012; *130:* 2359-2365.

[23] *Koh D-M, Collins DJ.* Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol. 2007; *188:* 1622-1635.

[24] *Bendell JC, Bekaii-Saab TS, Cohn AL, Hurwitz HI, Kozloff M, Tezcan H, Roach N, Mun Y, Fish S, Flick ED, Dalal D, Grothey A.* Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-bevacizumab or FOLFIRI-bevacizumab: results from ARIES, a bevacizumab observational cohort study. Oncologist. 2012; *17:* 1486-1495.

[25] *Carrato A, Swieboda-Sadlej A, Staszewska-Skurczynska M, Lim R, Roman L, Shparyk Y, Bondarenko I, Jonker DJ, Sun Y, De la Cruz JA, Williams JA, Korytowsky B, Christensen JG, Lin X, Tursi JM, Lechuga MJ, Van Cutsem E.* Fluorouracil, leucovorin, and irinotecan plus either sunitinib or placebo in metastatic colorectal cancer: a randomized, phase III trial. J Clin Oncol. 2013; *31:* 1341-1347.

[26] *Hecht JR, Trarbach T, Hainsworth JD, Major P, Jäger E, Wolff RA, Lloyd-Salvant K, Bodoky G, Pendergrass K, Berg W, Chen BL, Jalava T, Meinhardt G, Laurent D, Lebwohl D, Kerr D.* Randomized, placebo-controlled, phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK 222584, an oral vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. J Clin Oncol. 2011; *29:* 1997-2003.

[27] *Hoff PM, Hochhaus A, Pestalozzi BC, Tebbutt NC, Li J, Kim TW, Koynov KD, Kurteva G, Pintér T, Cheng Y, van Eyll B, Pike L, Fielding A, Robertson JD, Saunders MP.* Cediranib plus FOLFOX/CAPOX versus placebo plus FOLFOX/CAPOX in patients with previously untreated metastatic colorectal cancer: a randomized, double-blind, phase III study (HORIZON II). J Clin Oncol. 2012; *30:* 3596-3603.

[28] *Van Cutsem E et al.* A phase I/II, open label, randomized study of BIBF 1120 plus mFOLFOX6 compared to bevacizumab plus mFOLFOX6 in patients with metastatic colorectal cancer. Eur J Cancer. 2011; *47* (suppl)*:* 8-9. (LBA at the EMCC Stockholm 2011) (2011).

[29] *Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoephel A, Quant J, Heckel A, Rettig WJ.* BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008; *68:* 4774-4782.

[30] *Mross K, Stefanic M, Gmehling D, Frost A, Baas F, Unger C, Strecker R, Henning J, Gaschler-Markefski B, Stopfer P, de Rossi L, Kaiser R.* Phase I study of the angiogenesis inhibitor BIBF 1120 in patients with advanced solid tumors. Clin Cancer Res. 2010; *16:* 311-319.