Phase I/II trial of capecitabine and oxaliplatin in combination with bevacizumab and imatinib in patients with metastatic colorectal cancer: AIO KRK 0205

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Background: Combined inhibition of platelet-derived growth factor receptor beta signalling and vascular endothelial growth factor promotes vascular normalisation in preclinical models and may lead to increased delivery of chemotherapy to tumour tissue. This phase I/II trial assessed the safety and efficacy of capecitabine plus oxaliplatin (XELOX) plus bevacizumab and imatinib in the first-line treatment of patients with metastatic colorectal cancer.

Methods: Two dose levels (I/II) were defined: capecitabine 850/1000 mg m⁻² twice daily on days 1–14; oxaliplatin 100/130 mg m⁻² on day 1; bevacizumab 7.5 mg kg⁻¹ on day 1; imatinib 300 mg day⁻¹ on days 1–21 every 21 days. The primary study endpoint was safety. The phase II secondary endpoint was 6-month progression-free survival (PFS).

Results: Dose level I was chosen for phase II testing because, even though further dose escalation was permitted by the protocol, gastrointestinal toxicities were considered to be clinically significant. A total of 49 patients were evaluated. The 6-month PFS rate was 76%, median PFS was 10.6 months and median overall survival was 23.2 months. Haematological toxicities were generally mild. Sensory neuropathy and diarrhoea were the most common grade 3 toxicities.

Conclusion: The combination of XELOX with bevacizumab and imatinib is tolerable and has promising efficacy.

Chemotherapy with a fluoropyrimidine plus oxaliplatin or irinotecan combined with agents targeting the epidermal growth factor receptor in K-ras wild-type patients or vascular endothelial growth factor (VEGF) are regarded as standard of care in the treatment of patients with metastatic colorectal cancer (mCRC) (Van Cutsem et al, 2010). Recently, the potential benefits of continuing bevacizumab after disease progression (Grothey et al, 2008) have been confirmed by two phase III trials that showed...
prolonged progression-free survival (PFS) and/or overall survival (OS) with bevacizumab plus second-line chemotherapy vs chemotherapy alone (Masi et al., 2012; Bennouna et al., 2013). However, the clinical effects were smaller than expected from registration data. Additionally, the antibody construct aflibercept, which targets both VEGF and placental growth factor, improved PFS and OS in combination with chemotherapy vs chemotherapy alone when given as second-line therapy; a subgroup of patients who had received first-line bevacizumab showed a similar benefit (Van Cutsem et al., 2012). Based on these data, it is clear that anti-angiogenic therapy has an important role in mCRC but further improvements are needed.

VEGF receptor (VEGFR) signalling induces neoangiogenesis with a structurally chaotic vasculature characterised by increased leakiness and interstitial fluid pressure (IFP), which impair the delivery of cytotoxic agents to the tumour. Normalisation of the tumour vasculature is considered to be a key mechanism of action of VEGF-targeted therapies (Jain, 2005). Platelet-derived growth factor receptor beta (PDGFRβ) is expressed on different cell types in the tumour stroma (i.e. endothelial cells and pericytes). Accordingly, the PDGFRβ pathway is essential for recruiting perivascular cells during angiogenesis (Pietras et al., 2003). Preclinical models show that immature tumour vessels are more prone to the anti-angiogenic effects of VEGF-targeted treatment (Bergers et al., 2003) and that inhibition of PDGFRβ signalling decreases IFP (Pietras et al., 2002). Additionally, synergistic effects from the combined inhibition of VEGF and PDGFRβ signalling might be expected according to preclinical data (Klosowska-Wardega et al., 2009).

In principle, tyrosine kinase inhibitors (TKI) targeting both VEGFR and PDGFRβ (i.e., sunitinib) are available. However, TKI targeting VEGFR did not show clinical efficacy in mCRC (Sobrero and Bruzzi, 2011; Van Cutsem et al., 2011; Schmoll et al., 2012), and a phase III trial testing sunitinib plus 5-fluorouracil/leucovorin plus irinotecan (FOLFIRI) in mCRC was stopped early due to lack of clinical efficacy (Carrato et al., 2013).

Therefore, we sought to establish a combination therapy of bevacizumab with the TKI imatinib, a powerful inhibitor of PDGFRβ, and capecitabine plus oxaliplatin (XELOX) in a phase I/II trial. The clinical activity of imatinib in blocking PDGFRβ-signalling in perivascular cells has been demonstrated in patients with pulmonary arterial hypertension at doses of 200–400 mg day\(^{-1}\) (Ghofrani et al., 2005; ten Freyhaus et al., 2012) and a dose of 300 mg day\(^{-1}\) is supported by recent pharmacokinetic data (Michael et al., 2013). To the best of our knowledge, these are the first data on the tolerability/toxicity and clinical efficacy of this particular combination in patients with previously untreated mCRC.

**Study design.** Study AIO KRK 0205 was a prospective, non-randomized, open-label phase I/II clinical trial conducted in five centres in Germany within the Arbeitsgemeinschaft Internistische Onkologie (AIO) according to the Helsinki Declaration. The protocol was reviewed and approved by the local ethics committees of all participating centres; all patients gave written informed consent and the data were monitored by an independent data safety monitoring board (DSMB). The investigators designed, conducted and analysed the study independently. The trial was registered on ClinicalTrials.gov (identifier: NCT00784446).

The primary objective of phase I was to assess the tolerability, safety and dose-limiting toxicities (DLT) of XELOX plus bevacizumab and imatinib, and to define the recommended doses for phase II study. The phase II primary endpoint was safety and toxicity. Secondary endpoints were: Progression free rate at 6 months; objective response rate; PFS; OS, and rate of secondary resection of metastasis.

A cross-trial comparison of cycle numbers with study AIO KRK 0604 (Schmieg et al., 2013), which included XELOX plus bevacizumab as one study arm (n = 127), was also performed.

**Patients.** Eligible patients were aged ≥18 years, had previously untreated, histologically proven unresectable stage IV colorectal cancer. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status <2, and adequate renal, hepatic and haematological function. K-ras mutation status was determined as part of routine clinical practice and was available in 36 of 49 patients (73%).

**Chemotherapy.** All patients received combination therapy consisting of XELOX plus bevacizumab and imatinib. Bevacizumab was administered orally twice daily (bid) on days 1 (evening) to 15 (morning). Oxaliplatin was given intravenously as a 2-h infusion on day 1. Bevacizumab was given intravenously as a 30–90-min infusion on day 1. Imatinib was administered orally once daily on days 1–21. The treatment cycle duration was 21 days. Treatment was administered until disease progression or intolerable toxicity.

The following dose levels were defined for phase I dose escalation: dose level I, capecitabine 850 mg m\(^{-2}\) bid, oxaliplatin 100 mg m\(^{-2}\), bevacizumab 7.5 mg kg\(^{-1}\) and imatinib 300 mg day\(^{-1}\); dose level II, capecitabine 1000 mg m\(^{-2}\) bid, oxaliplatin 130 mg m\(^{-2}\), bevacizumab 7.5 mg kg\(^{-1}\) and imatinib 300 mg day\(^{-1}\).

Dose modifications were performed according to the study protocol to manage adverse events. For toxicities that led to the termination of one or two agents, only the following combinations were allowed: capecitabine + oxaliplatin ± bevacizumab; or capecitabine + bevacizumab ± imatinib. Monotherapy was not permitted.

**Assessments.** Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Dose-limiting toxicity (DLT) was defined as grade 3 or 4 leukopenia or neutropenia with complications (i.e. fever); grade 4 neutropenia or leukopenia or grade 3 or 4 thrombocytopenia lasting >7 days; grade 3 gastrointestinal toxicity (i.e. diarrhoea, mucositis) lasting >4 days despite adequate supportive care; all grade 4 gastrointestinal toxicities; grade 3 or 4 (in case of liver metastasis) hepatic toxicity; grade 3 or 4 acute or chronic sensory neuropathy; grade 3 hand-foot skin reactions; other organ toxicities of >2 in severity, with the exception of medically irrelevant events (i.e. alopeca etc.) and allergic reactions to bevacizumab. All toxicities resulting in discontinuation of study medication were also defined as DLT.

For the assessment of tumours, computed tomography scans were performed at baseline, 6 weeks after the first cycle and every 9 weeks thereafter during treatment. Responses were analysed by the investigators according to Response Evaluation Criteria In Solid Tumours (RECIST), version 1.0. Progression-free survival was defined as the interval between start of treatment and the occurrence of progression, diagnosis of a second cancer, or death from any cause. Overall survival was defined as the interval between start of treatment and death from any cause.

**Statistical considerations.** Dose escalation followed a 6 + 3 design, that is 6 patients were initially treated at dose level I. If 0–1 patients experienced DLT from this cohort, the next dose level was used. If 2–3 patients experienced DLT at dose level I, a further 3 patients were treated at this dose level. If 2–3 of 9 patients experienced DLTs at dose level I, dose level II was initiated.

In phase II, a one-step design according to Fleming (1982) was used and sample size calculation was based on the assumption that a 6-month PFS ≥75% was promising contrasting to a futile rate of
60%. Based on a type I error of $\alpha = 10\%$ and power of 80%, 44 patients had to be included in the study.

Analysis of all parameters was performed descriptively, giving frequencies, means, medians, ranges and confidence intervals (CI). Median PFS and OS were estimated using Kaplan–Meier methods and expressed with 95% CI.

For the cross-trial comparison of the number of cycles with AIO KRK 0604, a two-tailed Wilcoxon–Mann–Whitney $U$-test was used and Hodges–Lehmann estimator was applied to calculate the probability of a difference between trials.

### RESULTS

Fifty-one patients were enrolled between April 2008 and February 2010. Two patients were considered ineligible because of major protocol violations (discontinuation of chemotherapy after one cycle and withdrawal of informed consent, $n = 1$; pre-existing coronary heart disease, $n = 1$). Therefore, 49 patients were evaluable according to intention-to-treat (ITT) principles. Patient characteristics ($n = 49$) are given in Table 1.

**Treatment.** A total of 585 cycles of study treatment were administered (median 10, range 1–36). The median duration of treatment was 6.2 months (range 0.4–24.4). Dose reductions/discontinuation of drugs according to the combinations prespecified in the study protocol (see Patients and Methods) were required for oxaliplatin, capecitabine, imatinib and bevacizumab in 52 (9%), 53 (9%), 43 (7%) and 21 (4%) cycles, respectively. A simplified combination of capecitabine plus bevacizumab plus imatinib was applied in seven patients for a total of 44 cycles (median 3, range 1–17).

The cross-trial comparison revealed that the median number of cycles in the AIO KRK 0604 trial with XELOX plus bevacizumab was 8 vs 10 cycles in the present trial. In AIO KRK 0604, 15% of patients received $\geq 14$ cycles and 9% received $\geq 20$ cycles. In the present trial, 31% of patients received $\geq 14$ cycles and 16% of patients received $\geq 20$ cycles (Hodges–Lehmann estimator 0.575, 95% CI: 0.483–0.667, $P = 0.12$).

**Toxicity.** Dose level I was expanded to nine patients after two of the six initial patients developed grade 3 toxicity (diarrhoea/vomiting, $n = 1$; paraesthesia $n = 1$). One patient in the next cohort of three patients also developed grade 3 diarrhoea and vomiting. Thus at dose level I, three of nine patients experienced DLT. Despite the fact that further dose escalation was permitted according to the study protocol, the main toxicities at dose level I (diarrhoea and vomiting) were considered to be clinically significant by the DSMB. Dose level I was therefore chosen for phase II study for safety reasons despite the fact that the maximum-tolerated dose (MTD) was not formally reached.

In the total phase I/II study population, 49 patients were evaluable for toxicity. A summary of toxicities is provided in Table 2. Haematological toxicity was moderate with grade 3 neutropenia observed in one patient (2%) and grade 3 thrombocytopenia in two patients (4%). There were no grade 4 haematological toxicities; however, febrile neutropenia occurred in one patient. Gastrointestinal toxicities were more common; grade 3 diarrhoea developed in eight patients (16%) and vomiting in three patients (6%). Adjustments were required for oxaliplatin, capecitabine, imatinib and bevacizumab in 52 (9%), 53 (9%), 43 (7%) and 21 (4%) cycles, respectively.

### Table 1. Baseline demographics and clinical characteristics

| Age, years | Median (range) | 63.4 (43–82) |
|---|---|---|
| Gender, $n$ (%) | Male | 37 (76) |
| | Female | 12 (24) |
| ECOG performance status, $n$ (%) | 0 | 30 (61) |
| | 1 | 18 (37) |
| Primary tumor, $n$ (%) | Colon | 29 (59) |
| | Rectum | 20 (41) |
| (Neo) adjuvant therapy, $n$ (%) | Yes | 15 (30) |
| | No | 34 (70) |
| Metastatic sites, $n$ (%) | 1 | 12 (24) |
| | $\geq 2$ | 37 (76) |
| Risk group, $n$ (%) | Low (0–2 points) | 45 (92) |
| | High (3–4 points) | 3 (6) |

**Abbreviation:** ECOG = Eastern Cooperative Oncology Group.

### Table 2. Incidence of common adverse events (≥grade 2) and events of special interest for bevacizumab ($n = 49$)

| Toxicity | Grade 2 | Grade 3 | Total |
|---|---|---|---|
| Anaemia | 6 | 3 | 9 |
| Leukocytopenia | 11 | 1 | 12 |
| Neutropenia | 6 | 2 | 8 |
| Thrombocytopenia | 5 | 0 | 5 |
| Anorexia | 1 | 0 | 1 |
| Nausea | 14 | 1 | 15 |
| Vomiting | 9 | 3 | 12 |
| Diarrhoea | 6 | 8 | 14 |
| Fatigue | 14 | 3 | 17 |
| Hand-foot syndrome | 9 | 2 | 11 |
| Pain | 11 | 2 | 13 |
| Neurosensory events | 11 | 13 | 24 |
| Thromboembolic events | 1 | 2 | 3 |
| Vascular leak syndrome | 0 | 1 | 1 |
| Haemorrhage (gastrointestinal) | 0 | 1 | 1 |
| Haemorrhage/bleeding (other) | 1 | 0 | 1 |
| Hypertension | 2 | 0 | 2 |

*One patient developed febrile neutropenia.

*Grade 1/2 hypertension occurred in seven (14%) patients.
Grade 3 sensory neuropathy occurred in 13 patients (27%); no grade 4 toxicity was observed. The most common bevacizumab-related toxicity was grade 1/2 hypertension which occurred in seven patients (14%). Furthermore, there were three grade 2/3 thrombocytopenic events, and one patient developed grade 3 vascular leak syndrome. Hand-foot-skin reactions occurred in 21 patients (42%), but only 4% were grade 3 events. There were no treatment-related deaths.

**Efficacy.** Forty-nine patients were evaluable for efficacy. One patient had a complete response, 21 patients had partial responses, 20 patients had stable disease and 3 patients had progressive disease. In four patients, the response was unknown because of withdrawal of consent or other reasons (i.e. toxicity). Thus, the overall response rate (complete plus partial response) was 45% (22 of 49 patients), and the disease control rate (complete plus partial response plus stable disease) was 86% (42 of 49 patients) (Table 3). Potentially curative resections of metastases were performed in 4 out of 48 (8%) patients.

In the ITT population (\(n = 49\)), 37 (76%) patients were progression-free at 6 months. Median PFS (ITT population) was 10.6 months (95% CI 9.5–15.8 months; Figure 1). Median OS (ITT population) was 23.2 months (95% CI 18.8–31.1 months; Figure 1). Survival endpoints according to K-ras mutation status revealed a median PFS of 9.7 months in patients with K-ras wild-type tumours (\(n = 22\)) and 10.4 months in patients with K-ras mutated tumours (\(n = 14\)), and median OS of 26.7 and 24.1 months, respectively.

**DISCUSSION**

In this phase I/II trial, the safety and tolerability of a combination of XELOX with bevacizumab and imatinib was studied. This combination was chosen to provide improved anti-angiogenic activity by blocking both the VEGF and PDGFR\(\beta\) signalling pathways. A standard dose of bevacizumab was used, and a dose of imatinib 300 mg day\(^{-1}\) was applied based on the results of pharmacokinetic studies in patients with chronic myeloic leukaemia indicating that doses \(\geq 300\) mg daily are sufficient to inhibit PDGFR\(\beta\) signalling *in vivo* (Peng et al. 2004). Furthermore, clinical data from patients with pulmonary hypertension have shown that doses of 200–400 mg day\(^{-1}\) are sufficient to achieve PDGFR\(\beta\) inhibition *in vivo* (Ghofrani et al., 2005; ten Freyhaus et al., 2012). A formal pharmacokinetic assessment was beyond the scope of the current trial. However, a recent pharmacokinetic study of 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) with bevacizumab plus imatinib supports the imatinib dosing schedule (300 mg day\(^{-1}\)) (Michael et al., 2013). Further, dose reductions to 200 mg day\(^{-1}\) were required in only 7% of cycles in the present trial.

In the phase I part of the study, gastrointestinal toxicity was the main DLT (i.e. diarrhoea and vomiting) and dose level I was chosen for phase II because these toxicities were considered to be clinically relevant, despite the fact that the criteria for MTD had not formally been met. Dose level I included a 15% decrease in the dose of capecitabine and a 23% decrease in the dose of oxaliplatin compared to standard XELOX, while bevacizumab was used at a standard dose (7.5 mg kg\(^{-1}\) every 3 weeks). Haematological toxicity was infrequent. This contrasts with another phase I trial where imatinib doses of 400 and 600 mg day\(^{-1}\) were used together with FOLFOX-6 (Michael et al., 2013). Thus, the dose of imatinib 300 mg day\(^{-1}\) appears to be a good compromise between PDGF-inhibiting activity and toxicity. Gastrointestinal toxicity was more common. At the dose level used the incidence and grade of diarrhoea, vomiting and nausea was within the expected range compared to other phase II and III trials using XELOX plus bevacizumab (Saltz et al., 2008; Tol et al., 2009; Schmiegel et al., 2013). Grade 2/3 HFS occurred in 11 (22.4%) patients compared to a rate of 16% grade 3/4 HFS (Schmiegel et al., 2013) and 19.4% of grade 3/4 HFS (Tol et al., 2009) reported in other trial. Despite the reduced dose of oxaliplatin used, the frequency of grade 3 peripheral neuropathy (27%) was higher than in other clinical trials using oxaliplatin combinations plus bevacizumab. Another AIO trial recently reported a rate of 24% grade 3/4 polyneuropathy (Schmiegel et al., 2013) and in phase III trials rates of 18% (Saltz et al., 2008) and 10.4% (Tol et al., 2009) were reported, respectively. It remains unclear if combined VEGF and PDGFR\(\beta\) inhibition might be responsible for this effect by interacting with nerve function during oxaliplatin-induced neurotoxicity. This toxicity limits prolonged use of this combination during first-line treatment. Side effects related to bevacizumab (i.e. hypertension and thrombocytopenic events) were in the expected range, and the addition of imatinib did not appear to aggravate these events. The same was true for other side effects like fatigue.

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**Table 3.** Response rates according to RECIST guidelines (\(N = 49\))

| Response Type               | No. of Patients (%) |
|-----------------------------|---------------------|
| Overall response rate       | 22 (45)             |
| Disease control rate        | 42 (86)             |
| Complete response           | 1 (2)               |
| Partial response            | 21 (43)             |
| Stable disease              | 20 (41)             |
| Progressive disease         | 3 (6)               |
| No data*                    | 4 (8)               |

*Withdrawal of consent or discontinuation of treatment due to toxicity.

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**Figure 1.** Probability of PFS and OS.
Efficacy is promising with a 6-month PFS rate of 76%, a median PFS of 10.6 months and median OS of 23.2 months. These results compare favourably with the findings of a phase III trial (median PFS 9.4 months, median OS 21.4 months) that tested XELOX or FOLFIRI plus bevacizumab (Saltz et al., 2008), and are similar to another phase III trial (10.7 and 20.3 months, respectively) (Tol et al., 2009) and the German phase II trial AIO KRK 0604 (10.4 and 26.7 months, respectively) (Schmiegel et al., 2013) that both tested XELOX plus bevacizumab. It is important, however, to take into account that the XELOX doses were lower in the present trial. Furthermore, in a cross-trial comparison between AIO KRK 0604 (Schmiegel et al., 2013) and this trial, a statistical trend towards the application of more treatment cycles in the present trial was noted. This may also be related to the fact that the protocol of this trial allowed prespecified dose reductions and discontinuation of drugs (i.e. oxaliplatin) due to toxicity, and patients could benefit from continuation of a less-toxic regimen with capectabine plus bevacizumab/imatinib. In line with this, a phase I dose-escalation study using 5-fluorouracil plus imatinib in gastric cancer patients reported a favourable toxicity profile (Al-Batran et al., 2007).

It is of interest that results from trials using TKI for the inhibition of VEGF or combined inhibition of VEGF and PDGFRβ in mCRC were disappointing. In a Japanese phase II trial of FOLFIRI plus sunitinib in patients with mCRC, the median PFS was short (6.7 months) (Tsuij et al., 2012), and a phase III trial of FOLFIRI with or without sunitinib was stopped early due to lack of efficacy (Carrato et al., 2013). Besides differences in the toxicity profiles, an optimal ratio in blocking different angiogenic pathways may be required to achieve good clinical results. This may not have been the case for some TKI (i.e. sunitinib).

CONCLUSION

XELOX plus bevacizumab and imatinib at the doses defined is a clinically feasible regimen. Oxaliplatin-related neurotoxicity may be slightly aggravated by combined VEGF and PDGFRβ inhibition. Efficacy data are promising, especially in view of the reduced chemotherapy doses. Combined inhibition of VEGF and PDGFRβ using bevacizumab plus imatinib is a concept worth investigating in further clinical trials, especially as maintenance therapy in combination with a fluoropyrimidine alone.

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CONFLICT OF INTEREST

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