Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma

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Background: To investigate the safety/tolerability of the EGFR-antibody cetuximab when added to irinotecan/5-fluorouracil (5-FU)/folinic acid (FA) for first-line treatment in patients with metastatic colorectal cancer (mCRC).

Patients and methods: Twenty-one patients with untreated, metastatic, EGFR-expressing CRC received cetuximab 400 mg/m² as an initial dose, and thereafter 250 mg/m² weekly. In addition, patients received infusional 5-FU (24 h) in two dose levels (1500 mg/m², low 5-FU group, n = 6 or 2000 mg/m², high 5-FU group, n = 15), plus FA at 500 mg/m² and irinotecan at 80 mg/m², weekly × 6 q50d.

Results: Twenty patients were assessable for tolerability after the first cycle. There were no dose limiting toxicities (DLTs) in the low 5-FU group and three DLTs (20%) in the high 5-FU group (two patients with diarrhea grade 3 and one patient with diarrhea grade 4). In the low 5-FU group all six patients received >80% of the planned dose. In the high 5-FU group, seven of 14 patients (50%) received ≤80% of the planned chemotherapy dose during the first cycle due to dosage reductions whilst treatment delays occurred in 10/14 patients. During the whole study period, the common grade 3/4 adverse events were acne-like rash (38%) and diarrhea (29%). Chemotherapy did not affect the pharmacokinetics of cetuximab determined at weeks 1 and 4. Fourteen patients (67%, 95% CI 47% to 87%) had a confirmed response, and six (29%) had stable disease. Median time to progression was 9.9 months [lower 95% confidence limit (CL) 7.9, upper 95% CL not reached]. Median survival time was 33 months (lower CL 20, upper CL not reached). Four patients received secondary surgery with curative intent, and a fifth was potentially eligible for surgery but declined.

Conclusions: Addition of cetuximab to weekly infusional 5-FU/FA plus irinotecan is safe and first data suggest a promising activity. The 5-FU dose of 1500 mg/m² is recommended for further studies.

Key words: cetuximab, irinotecan, chemotherapy, metastatic colorectal cancer

Introduction

Until recently, 5-fluorouracil (5-FU) in combination with folinic acid (FA) was the recommended first-line treatment for metastatic colorectal carcinoma (mCRC). The combinations of irinotecan and oxaliplatin with 5-FU/FA have improved the response rate and progression-free survival of patients with CRC [1–6] and with additional effective second-line treatment has prolonged survival from 8 months in untreated patients [7] to about 20 months in the most active arms of recent studies [5, 6, 8–10]. However, despite these recent improvements, the prognosis of patients with inoperable mCRC remains poor and this has driven the development of new therapies that target the specific aberrations that are potentially involved in tumor cell proliferation and growth. Deregulation of epidermal growth factor receptor (EGFR) tyrosine kinase activity has been identified in many different human tumors including CRC, head and neck squamous cell carcinoma and non-small-cell lung cancer [11]. Over-expression of EGFR, or increased tyrosine kinase activity arising from mutations that cause its constitutive activation, or over-expression of EGFR natural ligands (epidermal growth factor or transforming growth factor alpha), can lead to cell proliferation, increased motility and protection against apoptosis, whilst inhibition of the EGFR pathway induces apoptosis and cell-cycle arrest and inhibits angiogenesis, tumor cell invasion and metastasis [12].

Cetuximab (Erbitux® Merck KGaA, Darmstadt, Germany/Imclone Systems Inc. Somerville, USA/Bristol-Myers Squibb

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Company, New York, USA), a humanized IgG1 monoclonal antibody, binds with high affinity to EGFR and blocks endogenous ligand binding. Preclinical studies showed that cetuximab reduced EGFR-dependent tumor cell proliferation in colon cancer tumor models [13, 14] and also inhibited angiogenesis [15]. Further preclinical investigations found that the addition of cetuximab to 5-FU, or irinotecan, or the irinotecan/5-FU/FA combination, demonstrated significant synergistic growth inhibition or tumor regression in HT29 and DLD1 colorectal xenograft tumors [16–18].

Cetuximab is active against metastatic mCRC after failure of irinotecan-based therapy. In second-, third- or higher-line treatment, cetuximab has yielded partial response (PR) rates of around 10% as a monotherapy [19, 20] and 23% when given in combination with irinotecan [19]. The apparent ability of cetuximab to overcome irinotecan resistance and to elicit a response in patients who have previously failed on irinotecan therapy, suggests a potential for increased efficacy when cetuximab is combined with an irinotecan-containing regimen in first-line therapy. Therefore, we performed a phase I/II trial that examined the feasibility of combining cetuximab with one of the most active combination schedules: the Arbeitsgemeinschaft Internistische Onkologie (AIO) infusional 5-FU/FA plus irinotecan regimen [6]. The aim of this trial was to explore the tolerability, safety, pharmacokinetics (PK) and efficacy of cetuximab plus irinotecan/AIO in the first-line treatment of EGFR-expressing, mCRC.

patients and methods

Patients were to be 18 years of age or older, with histologically confirmed, untreated stage IV colorectal carcinoma, a Karnofsky performance status ≥60, adequate hematological parameters (neutrophils ≥1500/mm³, platelet count ≥100 000/mm³, hemoglobin ≥8 g/dl and WBC ≥3000/mm³), renal and liver function [creatinine and bilirubin ≤1.5 upper normal level (UNL), ALAT and ASAT ≤5 × UNL]. A history of adjuvant chemotherapy was allowed if completed more than 6 months before entry to the study. At entry the patients had to have at least one unidimensionally measurable index lesion and immunohistochemical evidence of EGFR expression in either the primary tumor or a metastasis. EGFR expression was analyzed using the DakoCytomation, Hamburg, Germany) at a central pathology (Prof. S. Storkel, Wuppertal, Germany).

All patients had to provide written informed consent. The study protocol was approved by the ethics committees of the participating centers.

study design and treatment

This was an open-label, uncontrolled phase I/II trial conducted in three centers in Germany. All patients were treated with a combination of cetuximab plus irinotecan/5-FU/FA. A two-stage dose escalation procedure was used for the administration of 5-FU based on a modified AIO scheme. The increase from the low (1500 mg/m²) to high 5-FU dose (2000 mg/m²) was dependent on an acceptable frequency (i.e. less than two of six patients) of expected dose limiting toxicities (DLTs). The DLTs defined in the protocol were: leucopenia or neutropenia (grade ≥3), leucopenia or neutropenia with complications such as fever (grade ≥2), thrombocytopenia (grade ≥2), diarrhea (grade ≥2), mucositis (grade ≥2), skin toxicity (grade ≥3), any other organ toxicity (grade ≥2) but excluding medically irrelevant side-effects such as treatable nausea and vomiting, hair loss or taste alteration.

In week 1, cetuximab was given as a 2-h infusion at an initial dose of 400 mg/m² commencing with a test dose of 20 mg over 10 min and followed by a 30-min observation period to monitor for any systemic adverse reactions before continuation of the first dose. Further weekly doses of 250 mg/m² were given as 1-h infusions without a further test dose. A histamine receptor antagonist was administered immediately before all cetuximab infusions. There was a 1-h rest period following cetuximab administration after which irinotecan treatment was started as a 1-h infusion at a dose of 80 mg/m². FA was then administered as a 2-h infusion at a dose of 500 mg/m² and 5-FU was given as a 24-h infusion on an outpatient basis at the low- or high-dose as described above.

Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0.

chemotherapy

For any patient with diarrhea, mucositis or thrombopenia (grade ≥1), chemotherapy had to be delayed until grade 0 was achieved. For patients with other organ toxicity (except skin toxicity, medically irrelevant side-effects or asymptomatic increase of transaminases) or hand–foot syndrome grade ≥2, leucopenia or neutropenia grade ≥3, chemotherapy had to be delayed until grade ≤1 was achieved. For patients with leucopenia or neutropenia grade ≥3, neutropenia with fever or other organ toxicity grade ≥2, thrombocytopenia, mucositis, diarrhea, constipation grade ≥1, the chemotherapy had to be reduced to 80% of the previous dose for all further administrations. For patients with hand–foot syndrome grade ≥3, 5-FU had to be reduced to 80% of the previous dose for all further administrations.

cetuximab

Dosing was delayed in cases of skin toxicity grade ≥2 and was reduced to 200 mg/m² after a second occurrence of skin toxicity of grade ≥2, and to 150 mg/m² after a third occurrence of skin toxicity of grade ≥3. Cetuximab was stopped in cases of a fourth occurrence of skin toxicity of grade ≥3, or a delay in dosing for three consecutive weeks due to skin toxicity, or an allergic reaction grade ≥2.

The treatment schedule was designed to repeat the treatment (cetuximab plus chemotherapy) every week for 6 weeks to be followed by a 1-week period of cetuximab as monotherapy (the duration of one cycle was therefore 7 weeks in total). In cases where chemotherapy was delayed, the cycle was prolonged by 1 week per delay. Patients who completed at least one cycle, or stopped therapy before this because of intolerable toxicity, were eligible for inclusion in the assessments for dose finding, safety and PK. Treatment was permitted to continue until the patient progressed, experienced unacceptable toxicity, or withdrew consent.

trial assessments

Safety was assessed continuously throughout the trial by monitoring adverse events. Blood samples were taken every week for routine laboratory testing. The assessment of DLTs was performed during the first treatment cycle and was based on the NCI Common Toxicity Criteria (CTC) Version 2. Blood samples for PK analysis were taken before and after 1, 2, 5, 24, 48, 96 (optional) and 168 h after the first and fourth cetuximab infusions during the first treatment cycle.

The evaluation of efficacy was performed locally according to the Response Evaluation Criteria in Solid Tumors (RECIST) system [21] using computerized tomography (CT) or magnetic resonance imaging (MRI) technique at screening and at the end of each treatment cycle using the same method.

data analysis

Objective response was analyzed as described above. Time to progression (TTP) from the date of the first dose of cetuximab was estimated using the
Kaplan–Meier method with associated statistics. Descriptive summaries were presented for the safety data. The calculation of PK parameters was performed according to non-compartmental standard methods to include maximum serum concentration \((C_{\text{max}})\), time to maximum concentration \((t_{\text{max}})\), area under the curve from time zero to the last sampling time \((AUC_{0-t})\), apparent elimination rate constant \((k_{\text{e}})\), apparent terminal elimination half-life associated with the negative terminal slope \((t_{\frac{1}{2}})\), total body clearance of drug from plasma \((\text{CL})\) and the volume distribution at steady state \((V_{\text{ss}})\).

Cetuximab serum concentrations were determined using a validated sandwich enzyme-linked immunosorbent assay (ELISA), which was established at the bioanalytical facility of Merck KGaA in Grafing, Germany.

**results**

**patient population and treatment duration**

Twenty-seven patients were screened for EGFR-expressing tumors. In three tumor samples EGFR was undetectable. Three further patients dropped out of the study during the screening phase (one due to a pause in recruitment, one failed the inclusion criteria and one withdrew consent). Of the remaining 21, six patients received the low 5-FU dose and 15 patients received the high 5-FU. All patients were assessable for safety and efficacy. One patient who stopped treatment due to an inguinal abscess during the first cycle was not included in the analysis of dose intensity and DLT assessment.

The patients’ characteristics at study entry are presented in Table 1. The median age was 62 years and the majority of the patients were male \((n=16, 76\%)\). The median Karnofsky performance status was 100 and 24\% of the patients had received prior adjuvant therapy. Ten (48\%) patients had one metastatic site, nine patients (43\%) had two metastatic sites and two patients (10\%) had three or more metastatic sites.

The median treatment duration was 28.1 and 24.7 weeks in the low and high 5-FU dose groups, respectively. Fifteen patients withdrew from the study for reasons other than disease progression; four due to adverse events, five due to withdrawal of consent after three to five treatment cycles, one withdrew consent after CR and underwent secondary surgery, three due to surgical resection of metastases after PR and two due to other reasons.

**dose finding and safety**

None of the six patients in the low 5-FU dose group and three (20\%) patients in the high 5-FU dose group experienced a DLT (two patients with diarrhea grade 3 and one patient with diarrhea grade 4) during the first 7-week cycle of the study (Table 2). Therefore the predefined frequency of DLTs (more than two of six patients) was not reached in either the low or the high 5-FU dose groups.

There were no reductions of cetuximab dose but there were four instances of delayed cetuximab treatment in the high 5-FU group and one in the low 5-FU group during the first cycle, three due to severe acne and skin reaction, two due to diarrhea caused by chemotherapy (Table 3).

A reduction in the dose of chemotherapy (5-FU or irinotecan) was necessary during the first treatment cycle for seven of the

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<th>Table 1. Patient characteristics (eligible patients)</th>
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<td>Median age (years)</td>
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<td>Female</td>
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<td>Karnofsky PS</td>
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<th>Table 2. Incidence of adverse events during the first cycle</th>
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<td>Adverse events</td>
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<tr>
<td>Acne-like rash</td>
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<td>Cardiovascular events*</td>
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<td>Mucositis/stomatitis</td>
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<td>Nausea/vomiting</td>
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*Includes arrhythmia, heart failure, hemorrhage, and thromboembolism only.

*One event due to dosing error and not considered to be a dose-limiting toxicity according to investigator.

5-FU, 5-fluorouracil; PS, performance status.
14 assessable patients in the high 5-FU group, and one patient in the low 5-FU group (Table 3). In addition, the administration of chemotherapy was delayed in 10 patients in the high 5-FU group and in one patient in the low-dose group during the first treatment cycle (Table 3). Although the formal predefined criteria for DLT were not met for patients in the high 5-FU group, the combination of toxicity-related treatment delays and dose reductions resulted in substantially lower dose intensities than that planned in the protocol and were even lower than the dose intensities received by the low 5-FU group. Seven of the 14 patients in the high 5-FU dose group received ≤80% of the planned chemotherapy doses during the first cycle (Table 3). Consequently, the low 5-FU regimen is recommended for use in further studies.

The observed side-effects and their intensity for the whole study period occurred as would be expected (Table 4). Acne-like rash (100%), diarrhea (95%), nausea/vomiting (81%) and asthenia (76%) were the most commonly reported events. Leucopenia occurred in one-third of the patients in the high 5-FU dose group, but only one of these cases was considered to be severe (i.e. grade 3).

Of the common adverse events (Table 4), those classified as grade 3 or 4 were acne-like rash (38%), diarrhea (29%), cardiovascular events (20%) and nausea/vomiting (5%). Most of these were grade 3 events with grade 4 events being reported only as single incidences: one each for acne-like rash and diarrhea. The laboratory analyses revealed one case of lymphopenia grade 3. The relatively low number of patients in the low 5-FU dose group (n = 6) precludes meaningful inter-group comparison of the safety data. All 21 patients had at least one adverse event that was considered to be related to cetuximab therapy. Serious adverse events occurred in five patients (24%), of which three (14%) were considered to be related to cetuximab and 16 patients (76%) experienced at least one adverse event that was classified as a grade 3/4 toxic event (of which 13 (62%) were considered to be related to cetuximab). Overall, four patients had an adverse event leading to withdrawal of study therapy: low dose, two patients stopped as a result of skin toxicity plus fatigue; high dose, one patient’s withdrawal was due to an inguinal abscess and one patient stopped owing to diarrhea plus nausea/vomiting despite concomitant medication. The regimen was well tolerated with six (29%) and 12 (57%) patients experiencing adverse events that led to cetuximab dose reduction or delay, respectively. There were no patient deaths during the study period including the 30 days after discontinuation of treatment.

### Pharmacokinetic Analysis

The concentration-time profiles for cetuximab obtained in weeks 1 and 4 were effectively the same for the low and high 5-FU dose groups (Figure 1A, B). The PK of cetuximab was stable and did not alter from the first week of dosing to the fourth week of dosing (Figure 1C). Derived PK parameters were similar for the two treatment groups (Table 5). The mean values for the volume of distribution were consistent with the distribution of cetuximab in the vascular space. The similarity of the PK results for the low and high 5-FU dose groups indicated that varying the 5-FU dose had little appreciable effect on the PK of cetuximab (Figure 1A, B).

### Efficacy

All 21 patients were assessable for efficacy. Two patients, one from each dose group, showed a complete response to treatment. In addition, three patients in the low 5-FU dose group and nine patients in the high 5-FU dose group achieved...
a partial response (Table 6). In total, objective responses were observed in 14 out of 21 patients (67%, 95% CI 47% to 87%). Only one patient (5%), who was treated with 2000 mg/m² 5-FU, had progressive disease during the first cycle. By the end of the study period, five of the 21 patients had tumor progression. The median time to progression was 9.9 months [lower 95% confidence limit (CL) 7.9, upper 95% CL not reached], censored for 15 patients who stopped the study without PD. The small number of patients did not allow comparisons to be made between the treatment groups, but the difference between the two dose groups appeared to be small (Table 6). Median survival time was 33 months (lower CL 20, upper CL not reached) and nine patients were still alive in January 2005.

During the study, four patients had lesions that became resectable and underwent R0 resection of their liver metastases. A fifth patient, who had a resectable rectal primary tumor and non-resectable liver metastases at baseline, was offered surgery after the liver metastases had shown a major response. Biopsies of the rectal mucosa in the region, where the primary tumor had been formerly located, suggested a pathological complete remission of the primary tumor. However, the patient refused any operation and treatment was discontinued after a relatively long period (12 cycles). Two months later progressive disease was noted and treatment with cetuximab/irinotecan/5-FU/FA was reintroduced resulting in complete clinical response of the liver metastases after three treatment cycles. The patient continued to receive cetuximab monotherapy every 2 weeks for 6 months without further progression.
The anti-EGFR antibody cetuximab is active in patients with CRC and induces objective responses in 23% of irinotecan-failing patients when combined with irinotecan [19]. The synergistic effects of cetuximab and an irinotecan-containing regimen provided a rational for investigating such a regimen as first-line treatment in CRC. Irinotecan and infusional 5-FU/FA (AIO) is one of the most active regimens in first-line treatment of metastatic CRC inducing a response rate of 62% and providing a median overall survival of >20 months in a randomized EORTC-trial [6]. In the current study it was proposed that the maximum synergistic effect would be achieved by weekly administration of the chemotherapy with the antibody, although it was not known if such a schedule would be well tolerated.

According to the clinical data at the start of the study, only patients with EGFR-expressing/detectable tumors were enrolled into this study. Now, first results in patients with EGFR-non-detectable tumors suggest that cetuximab is active whether EGFR can be detected by current immunohistochemistry or not [23, 24].

The predefined number of DLTs was not reached which indicated that cetuximab could be added safely to the chemotherapy regimen at the lower 5-FU dose (1500 mg/m²). However, when the 5-FU dose was increased to 2000 mg/m², an unacceptably high incidence of diarrhea was found. During the entire study period 40% of patients who received the 2000 mg/m² 5-FU dose experienced diarrhea grade ≥3, which is a notably higher incidence than that observed in the recently completed EORTC trial (24% with irinotecan plus FA/5-FU at a dose of 2000 mg/m²) [6]. In addition, the toxicity of the cetuximab and chemotherapy combination resulted in frequent dose reductions and treatment delays (Table 3). Consequently, 50% of the patients in the high-dose group received less than 80% of the intended dose intensity during the first cycle, which was even less than the actually delivered dose in the low-dose group. It is for this reason that we would recommend the lower, 1500 mg/m² 5-FU dose for further studies.

In the pharmacokinetic analyses, the PK properties of cetuximab were unaffected by co-administration with 5-FU at the two different doses. Furthermore, there was no change in the PK parameters with prolonged dosing (comparison between weeks 1 and 4: Figure 1C). In an earlier study, the Cmax of cetuximab was estimated at 153 μg/ml (cetuximab monotherapy) and 162 μg/ml (cetuximab combined with irinotecan), with AUC0–t values of 13 039 μg/ml and 14 923 μg/ml, respectively [22]. These values compare well with the data from the current study. There was no change in the t½ value, neither between groups nor between time points, indicating that there was no accumulation of cetuximab. Thus, it is unlikely that there is any drug interaction in terms of metabolism or elimination.

In contrast to the EGFR tyrosine kinase inhibitors, like gefitinib, that are known to induce diarrhea in a dose-dependent manner when used as monotherapy [25, 26], diarrhea grade ≥3 is an uncommon event with cetuximab monotherapy and occurs in around 2% of cases [19, 20]. However, the possibility that the combination of cetuximab with chemotherapy slightly increases the rate of diarrhea cannot be excluded. In addition to the findings of our study, an investigation of cetuximab in combination with the IFL-regimen (irinotecan, FA and bolus 5-FU) also reported a high incidence of diarrhea and recommended a lower dose of chemotherapy due to a large number of dose reductions [27]. By comparison, no reduction in the dose of chemotherapy was required when cetuximab was combined with the simplified biweekly FOLFIRI schedule (5-FU, FA, irinotecan) [28] or the biweekly FOLFOX4 regimen (5-FU, FA, oxaliplatin) [29]. In combination with FOLFOXI, neither diarrhea grade 3/4 (14%) nor leucopenia grade 3/4 (19%) were more frequent when compared with data from randomized studies [9]. These differences may be explained by the fact that the simplified FOLFIRI and FOLFOX4 regimes are, in any case, associated with a lower frequency of diarrhea grade 3/4 (14% [9] and 12% [1]) than IFL (23% [4]) or irinotecan/5-FU/FA(AIO) (29% [6]).

One of the major tolerability issues associated with EGFR-targeted therapies is the development of an acne-like rash. Overall, we observed skin toxicity grade ≥3 in 38% of patients (Table 4) which is higher than that reported with cetuximab in recent trials (7%, 12.7% and 17.6%) [19, 20]. This is probably an effect of the longer treatment duration in our trial (24 and 28 weeks in the high- and low-dose groups, respectively) compared with the earlier studies in more advanced tumors where tumor progression (an end point for treatment cessation) was observed after a median time of 6 and 17 weeks with cetuximab mono- or combination therapy, respectively [19]. During the first 7-week cycle of the current study, skin toxicity grade ≥3 was observed in only 14% of patients (three of 21; Table 2), which corresponds closely with the shorter treatment periods of the previous study. The low number of patients in our study did not allow an examination of the relationship between survival or response rate and the incidence of skin toxicity.

As with all antibody-based therapy there is a low risk of allergic reaction and with cetuximab overall reported incidences have ranged from 2% to 4% with treatment discontinuation necessary in severe cases [19, 20, 30]. There were no cases of allergic reaction or hypersensitivity grade ≥3 in this study that led to the discontinuation of cetuximab therapy.

The efficacy of treatment with cetuximab and irinotecan/infusional 5-FU/FA (AIO) is promising with an overall response rate in this trial of 67% (Table 6). Although the data presented here are from a relatively small phase I/II study, and the patients had a rather favourable performance status, the response rate suggests that the addition of cetuximab could improve efficacy over the 62.2% (CR + PR) reported for the irinotecan-based AIO regimen (5-FU) in a recent phase III study [6]. Higher, unconfirmed, preliminary response rates of up to 81% have been reported in patients with CRC when cetuximab is added to the FOLFOX4 regimen [29] or a simplified FOLFIRI-schedule [28]. Furthermore, although patients with widespread mCRC were included in our trial (i.e. patients were not excluded if they had metastases at sites other than the liver), four patients underwent secondary resection of their liver metastases. This illustrates the potential for the cetuximab plus irinotecan/5-FU/FA (AIO) combination to induce a response: this is especially important in this subgroup of patients with non-resectable liver metastases. In addition, the median time to
tumor progression of 9.9 months seen here with the inclusion of cetuximab, indicates that this regimen could extend the disease-free period over the 8.5 months reported for the irinotecan plus AIO chemotherapy regimen [6].

This study demonstrated that cetuximab in combination with irinotecan and infusional 5-FU (1500 mg/m²)/FA is a feasible and well tolerated regimen. With the limitation of a small sample size, we observed promising activity for the combination of the anti-EGFR antibody cetuximab with irinotecan/infusional 5-FU/FA (AIO). Also based on the promising results of this study, a phase III program has been started that investigates the addition of cetuximab to irinotecan plus infusional 5-FU/FA (i.e. CRYSTAL study).

acknowledgements

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