Gy over a period of approximately 6 weeks. Capecitabine was given at an oral dosage of 825 mg/m* bid on each day of the radiotherapy period (the recommended dose from the phase-I-study), with the first daily dose applied two hours before irradiation. Up to now, 45 patients (pts) (60% male, 40% female) have been recruited from 6 university clinics in Germany since June 2001. Mean age was 64 years, with an unimpaired performance status (ECOG 0) in 55%. Clinical staging revealed T3 and T4 tumors, respectively, in 50% of the cases, each, and involved lymph nodes (cN+) in 53%. In 81% of the pts, the radiochemotherapy induced a clinical complete or partial remission, leading to a similar rate of R0 resections. The comparison of initial diagnosis and pathological findings showed a downstaging in 72% of pts, mainly from cT4 to pT3 ñ pT0. Only 8% remained inoperable at the end of the irradiation period. Safety findings were concordant to the phase I results with >10% incidence of NCI grade 2/3 only in leukopenia (22%), anemia (13%), skin (15%) and diarrhea (17%). The concurrent combination of radiotherapy and continuous daily capecitabine proved to be well tolerated in a multicenter setting and showed major clinical response in the vast majority of the patients.

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Evaluation of thymidine phosphorylase, dihydropyrimidine dehydrogenase and thymidylate synthase mRNA levels in colorectal cancer reveals significant correlations to tumor histopathology and disease-free survival in 5-FU treated patients

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Purpose: Evaluation of three mediators of pyrimidine metabolism - thymidine phosphorylase (TP), dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS) - in colorectal cancer (CRC) as markers of prognosis and/or response prediction to 5-fluorouracil (5-FU) chemotherapy (CTX).

Materials and Methods: RNA was isolated from microdissected tumor areas of formalin-fixed and paraffin-embedded CRC tissues and subjected to quantitative RT-PCR in the LightCycler® system. RT-PCR data was correlated to tumor histology (n=102), patient prognosis ("no CTX"/ n=40 and "CTX" / n=52) and the clinical response to adjuvant 5-FU CTX (n=52).

Results: Significant correlations were found for tumor 1) T and N category and UICC stage (TP mRNA, TP:DPD ratio), 2) T category (TS:DPD ratio), and 3) differentiation grade (TS mRNA and TS:DPD ratio). Moreover, whereas overall survival was correlated to the TS:DPD ratio in the "no CTX" group (p=0.032), neither TP, DPD and TS mRNA nor the TP:DPD ratio had any prognostic impact in this group. However, both DPD and the TP/DPD ratio were correlated to disease-free survival in 5-FU treated patients, with p=0.05 and p=0.002, respectively.

Conclusion: We present a novel, high throughput approach for TP, DPD and TS mRNA quantification in archival, microdissected tissue specimens. Besides a significant correlation of TP, DPD and TS mRNA expression with tumor histology and stage, the TS:DPD ratio may represent a prognostic marker in colorectal cancer patients treated with resection alone. Moreover, DPD mRNA expression and the TP:DPD ratio were identified as potential predictive markers for disease-free survival in adjuvant 5-FU treated colorectal cancer patients.

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DCC protein expression in colorectal cancer (CRC) metastases and lack of response to biochemically-modulated 5-fluorouracil (FU) among patients (pts) with low level of thymidylate synthase (TS) protein expression

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TS protein expression in CRC metastases has been shown to predict for the clinical response to FU in multiple studies. However, this correlation is not absolute as 1/3 of the pts with low TS levels fail to respond to FU-based chemotherapy (CT). Since the absence of the DCC protein has been shown to convey a poor prognosis to pts with resected CRC and DCC status may affect drug sensitivity, we have investigated whether assessment of DCC expression in CRC metastases could improve response prediction identifying pts that will not respond to FU despite low levels of TS expression. DCC and TS protein were retrospectively analysed by immunohistochemistry on archival, formalin-fixed, paraffin-embedded tumor samples from 41 pts with unresectable metastatic CRC homogeneously treated with a regimen alternating bolus and infused 5-FU with schedule-specific biochemical modulators. Positive immunostaining was detected in 19 out of 41 pts (46%). DCC status was not related to the level of TS expression (high TS: 10/22, 45% versus 9/19, 47%, in DCC negative and positive tumors, p=0.90). Consistently, the mean/median TS score was 1.95/2 and 2.21/2, in DCC negative and positive tumors (p=0.54). The proportion of pts responding to CT was not significantly different between tumors with DCC deletion and those expressing DCC (35% vs 52%, p=0.24). However, among the 22 pts with low TS, 8 out of 10 expressing DCC responded to CT as compared to 5/12 pts with DCC negative tumors (response rate 80% vs. 42%, p=0.06). 7 out of 9 pts with low TS that failed to achieve an objective response had a defective DCC protein expression in their tumors. Although statistical significance was not reached, the improvement in response prediction associated with DCC assessment was specific for the subgroup of pts with low TS expression. DCC status was not related to tumor response, time-to-progression (TTP) or survival (OS) among pts with high TS. Expression of DCC was also associated with a longer TTP and OS in the whole cohort of pts (8.3 vs 7.2 months, p=0.06 and 21.4 vs 14.3, p=0.05, respectively) but the rates of objective responses were similar in the two groups (35% vs. 52%, p=0.24). These data indicate that DCC maintains its prognostic value in advanced CRC and suggest that the poor prognostic features of tumors without DCC expression may overcome the favorable condition of a low level of TS expression accounting, at least in part, for the therapeutic failures observed in this group.

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Capecitabine and Mitomycin C (MMC) is an active well-tolerated regimen as first line treatment for metastatic colorectal cancer (MCRC).

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The combination of MMC and protracted venous infusion (PVI) 5FU has demonstrated superior efficacy compared to PVI 5FU alone as initial therapy in MCRC. Due to potential synergy based on upregulation of thymidine phosphorylase by MMC coupled with non-overlapping toxicity profiles capecitabine and MMC could enhance these results further. This phase II study was designed to evaluate the safety and efficacy of capecitabine in combination with MMC as first line treatment in MCRC.

Methods: Eligible patients were required to have WHO performance status (PS) 0-2, measurable disease, written consent, received no prior lines of palliative chemotherapy or adjuvant chemotherapy within the previous 6 months. Capecitabine (1250 mg/m2) was given twice daily for 14 days followed by 7 days rest, every 3 weeks, and MMC (7mg/m2 IV bolus) was given once every 6 weeks, maximum of 4 injections. CT response assessment according to RECIST criteria took place at 12 and 24 weeks.

Results: 64 patients have been accrued and complete toxicity and response data are available for 61 and 62 patients respectively. Median age 69 (range 29-82) years, PS was 0, 1, 2 in 36%, 58%, and 6% of patients. 55% of patients had more than 2 sites of disease. Overall response rate was 36% [95% CI: 24.3- 48.9] and 28% of patients had stable disease. Grade 3-4 toxicities were diarrhoea 12.5%, hand foot syndrome 22%, nausea and vomiting 3%, neutropenia 5%, and stomatitis 0%. Median failure free survival was 7 months.

Conclusion: Capecitabine and MMC has significant activity and a relatively favourable toxicity profile for previously untreated patients with MCRC.