patients (pts) with metastatic colorectal cancer (mCRC). PTK/ZK is a novel, oral, angiogenesis and lymphangiogenesis inhibitor that blocks tyrosine kinase signaling from all known VEGFRs.
Methods: This trial determined the maximum tolerated dose and dose-limiting toxicity (DLT) of once-daily oral PTK/ZK in combination with infusional 5-fluorouracil (5-FU)/leucovorin (LV) plus irinotecan (FOLFIRI) as first-line treatment in pts with mCRC. PTK/ZK was administered orally, once daily in escalating doses of 500, 1,000, 1,250, and 1,500 mg/day to cohorts of 3 to 7 pts. FOLFIRI was administered every 2 weeks as irinotecan (180 mg/m^2, day 1) plus LV (200 mg/m^2, 2-hour infusion) and 5-FU (400 mg/m^2 bolus followed by 600 mg/m^2 as a 22-hour infusion) on days 1 and 2.
Results: To date, 21 pts have been enrolled at 500 (n = 6), 1,000 (n = 7), 1,250 (n = 5), and 1,500 (n = 3) mg/day. PTK/ZK was well tolerated; commonly reported grade 1/2 adverse events were nausea, diarrhea, fatigue, vomiting, epistaxis, and dizziness. There was 1 DLT at 500 mg/day (grade 3 fatigue) and 1 at 1,000 mg/day of PTK/ZK (grade 3 hypertension); both resolved within 2 weeks of PTK/ZK discontinuation. The pharmacokinetics of PTK/ZK was unaffected by FOLFIRI. Coadministration of 1,250 mg/day PTK/ZK with FOLFIRI had minimal effect on irinotecan exposure, but lowered the area under the curve (AUC) of the active metabolite SN-38 in serum by ~40%; the clinical relevance is under investigation. Best response (by Southwest Oncology Group [SWOG] criteria) to date for 20 evaluable pts included 11 (55%) partial responses, 7 (35%) had stable disease, and no pts had progressive disease; 2 pts were not evaluable. Median progression-free survival for 20 pts was 7.1 months (95% CI = 6.2, 11.7 months).
Conclusion: These preliminary results suggest that the combination of PTK/ZK with FOLFIRI is safe, well tolerated, and has activity in pts with mCRC. Based on these findings, the 1,250 mg/day dosing cohort will be expanded by 24 pts.

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Topography and natural history of pelvic recurrences from rectal cancer treated with preoperative chemoradiation and intraoperative presacral electron boost

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Purpose: To analyze the pelvic anatomic pattern of recurrence and its clinical behaviour in rectal cancer intensively treated with neoadjuvant chemoradiation (CRT), radical surgery and adjuvant presacral intraoperative electron boost.
Patients and methods: From 5/1995 to 3/2003 154 consecutive patients (p) entered in the IOERT institutional adjuvant program for locally advanced rectal cancer (85% T_3, 10% T_4, 45% N_+). Preoperative treatment consisted in 4500–5040 cGy pelvic radiation with simultaneous 5FU iv continuous infusion (45 p), oral Tegafur 1200 mg/day (65 p), or two courses of neoadjuvant Oxaliplatin+5FU (FOLFOX4) followed by concomitant CRT with oral Tegafur (47 p). Radical surgery was performed 4–6 weeks after the completion of CRT. IOERT was delivered to all of patients over the presacral space, using circular applicators from 5 to 9 cm (beveled end angles of 30º and 45º degrees). The IOERT doses ranged from 1000 to 1500 cGy (mean 1250 cGy). Adjuvant systemic chemotherapy was electively administered to 66% of patients.
Results: Median follow-up time for the entire group was 40 months. Pelvic recurrences had been pathologically documented in 10 p (6%), 5 p were $_pT_3$ stages and 4 p were $_pN_+$ stages. Median time for pelvic recurrence diagnosis was 25 months (range 7 to 52 months). Anatomic topography within the pelvic area was: presacral (2), anastomotic (6), posterior vaginal wall (1) and hypogastric nodes (1). Timing of pelvic recurrences identified 4 isolated relapses, 1 sincronous (lung metastases) and 5 methacronous (liver, lung, retroperitoneum and CNS metastases). Rescue treatment for local relapses was atempted in 4 p. Outcome of p with local recurrences showed 2 p alive with disease (at 33 and 89 months), 1 p NED after surgical rescue (at 56 months) and 7 cancer related deaths.
Conclusions: Moderate Intraoperative presacral electron boost in the context of preoperative CRT minimizes the risk of topographic recurrence in the posterior pelvic cavity (1%), whereas peri-anastomotic tissues emerge as the new dominant site for pelvic recurrence (60%), offering potential opportunities for rescue treatment of radical intent.

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A phase II trial of Capecitabine (X) and Irinotecan (I) in a biweekly schedule in patients with untreated advanced colorectal cancer (ACRC)

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Background: Capecitabine (X) and Irinotecan (I) combination has been shown to be synergistic in ACRC. We conducted a phase II study of IX combination for previously untreated patients with measurable ACRC to evaluate the objective response rate and the safety profile. Secondary objectives were time to progression (TTP) and overall survival (OS).
Methods: Patients with histologically confirmed locally advanced or metastatic CRC, measurable disease, ECOG PS ⩽2 and adequate bone marrow, renal and hepatic functions were included. Previous adjuvant chemotherapy was allowed if finished ⩾6 months before starting study treatment. Patients received I 175 mg/m^2 on D1 as a 30-min iv infusion and X 1000 mg/m^2 twice daily po from D2–8. For patients >65 years, the dose of I and X were reduced to 140 mg/m^2 and 750 mg/m^2 twice daily, respectively. Cycles were repeated every 14 days until progressive disease, unacceptable toxicity or consent withdrawal.
Results: 45 patients were enrolled (M/F, 35/10). Median age was 67 y (42–80). Twenty-five (56%) patients were >65 y. ECOG PS 0–1: 93% of patients (42/45). Primary tumor sites were colon 51% (n = 23), rectum 47% (n = 21) or both 2% (n = 1). Median number of metastatic lesions was 2 (64% with ⩾2 sites) in liver (64%), lung (27%), peritoneum (13%), lymph nodes and bone (7%) and skin (3%). Previous treatment included surgery (73%), adjuvant chemotherapy (44%) and radiotherapy (20%). To date, 408 cycles (median 10, range 2–12; ⩽65/>65 184/224) were administered. Median relative dose intensity was 94% for X and 99.5% for I (85 and 99%, respectively, for patients >65 y). All patients were evaluable for toxicity (see table below). 38 pats have been evaluated to date: 3 achieved CR (7.9%, 2–21%), 16 PR (42.1%, 26–59%), 14 SD (36.8%, 22–54%) and 5 progressed (4–28%) resulting in an ORR of 50% (CI 95%: 33–67) and tumor growth control (RR + SD) in 87% of patients (CI 95%: 72–96). Median TTP and OS were not achieved yet.
Conclusions: X and I, in a biweekly schedule as first line treatment of locally advanced or metastatic CRC is an active schedule with a manageable toxicity profile, even in patients >65 years.

Toxicity gd. 3–4	Pat. ⩽ 65 (184 cycles)	Pat. >65 (224 cycles)
Thombopenia	0	1 (0.5%)
Neutropenia	2 (1.1%)	2 (0.9%)
Alopecia	5 (2.7%)	0
Nausea and vomiting	0	3 (1.3%)
Diarrhea	1 (0.5%)	7 (3.1%)
Asthenia	3 (1.6%)	9 (4.0%)
Other	2 (1.1%)	4 (1.8%)

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Cetuximab plus oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) for the epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer (mCRC) in the first-line setting: a phase II study

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Background: The EGFR is highly expressed in mCRC and is commonly associated with more aggressive disease and resistance to radiotherapy. Cetuximab (Erbitux®) is an IgG1 monoclonal antibody (MAb) that specifically targets the EGFR. FOLFOX-4 is a standard option for the first-line treatment of mCRC. The aim of this phase II study was to investigate

the safety and efficacy of combining cetuximab and FOLFOX-4 in EGFR-expressing mCRC in this setting.
Materials and methods: Patients with non-resectable EGFR-expressing mCRC, who had not received previous chemotherapy, were treated with cetuximab (400 mg/m^2 week 1 and 250 mg/m^2 weekly thereafter) plus FOLFOX-4 (every 2 weeks: oxaliplatin 85 mg/m^2, day 1; FA 200 mg/m^2 IV 2h and 5-FU 400 mg/m^2 IV bolus followed by 600 mg/m^2 IV for 22 h, days 1 and 2) until progressive disease or unacceptable toxicity.
Results: Of the 62 patients enrolled, 52 (84%) had EGFR-expressing disease. Among 42 evaluable patients, there was an objective response rate of 81% (34/42), with 4 complete (CR) and 30 partial responses (PR). The disease control rate (CR+PR+stable disease) was 98%. The median duration of response (n = 31) was 330 days (10.9 months) and the median progression-free survival (PFS) was 12.3 months, with a 12-month PFS rate of 52%. 4 patients remain on treatment. 9 patients (21%) with initially unresectable metastases underwent surgery with curative intent. In 8 of these, complete resections (R0) were achieved. Treatment was well tolerated and there were no unexpected toxicities. The main grade 3/4 adverse events observed per patient were: neurotoxicity and acne-like rash (30% each), diarrhoea (26%), neutropenia (21%) and asthenia (9%). There were no cetuximab-related deaths.
Conclusions: This study shows that combining FOLFOX-4 with cetuximab is safe and active in the first-line treatment of EGFR-expressing mCRC. In addition to achieving high response and disease control rates, the combination enabled one-fifth of patients to undergo resection of liver metastases. A simplified independent read is in process to provide an objective review of the responses reported by the investigators. The results of independent read will be presented at ECCO.

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Clinical benefit of bevacizumab in responding and non-responding patients with metastatic colorectal cancer

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Background: Bevacizumab (Avastin™), a monoclonal antibody to vascular endothelial growth factor (VEGF), is a potent anti-angiogenic agent with demonstrated survival benefit in first- and second-line metastatic colorectal cancer (mCRC), in combination with 5-FU/irinotecan or 5-FU/oxaliplatin. Because preclinical data suggest bevacizumab is primarily a cytostatic agent, we explored the clinical benefit of bevacizumab assessed by progression-free survival (PFS) and overall survival (OS) in responding and non-responding subgroups.
Methods: In the pivotal trial, 813 patients with untreated mCRC were randomized to receive irinotecan, 5-FU, and leucovorin (IFL) plus either bevacizumab or placebo. For this retrospective, exploratory analysis, patients were divided into two groups; "responders" and "non-responders", which includes stable disease patients who remained on protocol therapy at day 180 without achieving a partial response/complete response or progressive disease, as well as patients who went off therapy within the first 180 days without a RECIST compliant tumor assessment. For all analyses, PFS and OS within subgroups were estimated from Kaplan-Meier curves, and hazard ratios (HRs) for progression and death were estimated by Cox regression.
Results: The bevacizumab and placebo arms in both the responding and non-responding subgroups had similar baseline characteristics. Statistically significant improvements in HR for PFS and overall survival for bevacizumab-treated patients were observed in both subgroups (Table 1) and were consistent between the groups (interaction *P*-value for overall survival = 0.44; for PFS, 0.73).

Table 1

Best response	Treatment	n	OR		PFS	
			HR	95%CI	HR	95%CI
All Subjects	Bevacizumab + IFL	402	0.66	0.39–0.84	0.54	0.45–0.66
	Placebo + IFL	411				
Responders	Bevacizumab + IFL	180	0.60	0.40–0.90	0.53	0.38–0.74
	Placebo + IFL	143				
Non-responders	Bevacizumab + IFL	222	0.76	0.60–0.96	0.63	0.49–0.80
	Placebo + IFL	268				

Conclusions: These analyses suggest that the magnitude of clinical benefit associated with bevacizumab treatment, as measured by HR for PFS and OS, is similar in mCRC, regardless of objective tumor response. This response-independent survival benefit is a novel observation in mCRC, and has implications for endpoint selection in bevacizumab-based clinical trials and the routine clinical use of bevacizumab. Data suggest that strategies of discontinuing bevacizumab in patients without an objective tumor response or at the time of maximal tumor response may compromise overall clinical benefit with respect to PFS and OS.

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Plasma levels of tissue inhibitor of metalloproteinases 1 (TIMP-1) and tumor type M2 pyruvate kinase (TuM2-PK) for monitoring of advanced colorectal cancer

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Purpose: Recently, a high expression of tissue inhibitor of metalloproteinases 1 (TIMP-1) was demonstrated by immunohistochemistry in colorectal cancer. TIMP-1 can also be detected in plasma of those patients. We investigated the longitudinal levels of TIMP-1 in 37 patients with advanced colorectal cancer (CRC) and correlated the monitoring performance of TIMP-1 in comparison to CEA and CA19−9 as established markers of tumor load for colorectal cancer, and to the plasma level of tumor type M2 pyruvate kinase (TuM2-PK) as marker of disease activity.
Material and methods: Plasma TIMP-1 (Bayer Diagnostics, Tarrytown/NY) and TuM2-PK (Schebo Biotech, Giessen, Germany) levels were measured using standardized ELISA assays while serum CEA and CA19−9 were determined using chemiluminescent immunoassays (Bayer Diagnostics, Tarrytown/NY). The nonparametric analysis of variance for repeated measurements by Brunner was used to test for time effects between the selected 3 time points: baseline at initiation of systemic chemotherapy for metastatic disease, best response and later progression.
Results: We grouped 37 patients with regard to best response to chemotherapy as follows: CR/PR: n = 10; SD: n = 21; PD: n = 6. TIMP-1 and TuM2-PK concentrations increased significantly from baseline to progression ($p < 0.001$ and $p = 0.003$, respectively). The plasma levels of patients with objective response (CR/PR) dropped significantly ($p = 0.001$) for TuM2-PK and TIMP-1 ($p = 0.001$), while CA19−9 ($p = 0.943$) and CEA ($p = 0.097$) did not change significantly. No significant change could be demonstrated in the SD group for TuM2-PK ($p = 0.261$), TIMP-1 ($p = 0.694$) and for CEA ($p = 0.248$), whereas CA19−9 concentrations decreased significantly ($p = 0.037$).
Conclusion: Innovative markers like TIMP-1 and TuM2-PK provided a much higher monitoring quality than established markers like CEA and CA19−9 in colorectal cancer. As the later cancer-associated proteins are recommended by internationally acknowledged guidelines, larger comparative trials are warranted. Combined data of TIMP-1 and TuM2-PK in the form of scoring algorithms will be presented.

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Cost-effectiveness analysis of oxaliplatin/5-FU/LV in adjuvant treatment of stage III colon cancer in Germany

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Background: The MOSAIC trial demonstrated that oxaliplatin/5-FU/LV (FOLFOX4) as adjuvant treatment of stage II/III colon cancer significantly improves disease-free survival (DFS) at 4 years, compared to 5-FU/LV (69.7% vs. 61.0%, p = 0.002)[1]. This analysis evaluates the long-term cost-effectiveness of using FOLFOX4 in this setting, from the German public health payer perspective.
Methods: We estimated the cost per life-year (LY) gained over a lifetime. Using stage III patient data from the MOSAIC trial (median follow-up 44.2 months), we estimated DFS and overall survival (OS) up to 4 years from randomization. We extrapolated DFS from 4 to 5 years by fitting a Weibull model, and thereafter using a life table for the US general population. We assumed no relapse occurred beyond 5 years. We predicted OS beyond 4 years using the extrapolated DFS estimates and observed survival after relapse. Costs were calculated from trial data up to relapse, accounting for censoring; while for periods after relapse or 4 years they were estimated using literature. Uncertainty was explored using a bootstrap approach.
Results: The extrapolated life-expectancy of stage III patients on FOLFOX4 was 17.51 years vs. 16.18 years for patients on 5-FU/LV. The lifetime extrapolated incremental DFS between FOLFOX4 and 5-FU/LV was 1.98 years (95% confidence interval: 0.65−3.31). The expected cost of