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.

643 POSTER

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

treatment following relapse was close to *21,000 in both arms. Total lifetime disease-related costs were *23,129 with oxaliplatin vs. *17,285 with 5-FU/LV. The resulting incremental cost-effectiveness ratio for FOLFOX4 compared to 5-FU/LV was *9,328 per LY gained, after discounting costs and outcomes at 5% per annum.
Conclusions: Adjuvant chemotherapy with FOLFOX4 has shown a significant DFS benefit over 5-FU/LV in the MOSAIC trial. We extrapolated the within-trial data to estimate a 1.34 (−0.01–2.68) year benefit in overall life expectancy in patients with stage III disease. If this benefit is confirmed, we estimate that FOLFOX4 would cost approximately *9,300 per LY gained, which compares favourably with other accepted interventions in oncology.

References

[1] De Gramont, 2005 ASCO Annual Meeting, Abstract 3501

646 POSTER

Phase I/II study of preoperative cetuximab, capecitabine and external beam radiotherapy in patients with locally advanced rectal cancer (LARC)

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Background: Capecitabine is rapidly replacing 5-fluorouracil as the standard agent in colorectal treatment regimens for locally advanced rectal cancer (LARC). Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor. Both agents are active in the treatment of advanced colorectal cancer and have demonstrated radiosensitising properties. The aim of this study was to establish the feasibility of a combination of weekly cetuximab and daily capecitabine with concurrent radiation for patients with LARC. Previous studies have shown that the Recommended Dose of Capecitabine in combination with radiation for LACR is 825 mg/m^2 twice-daily.
Material and Methods: Ten patients with LARC (T3–T4 and/or N+) received radiotherapy (1.8 Gy, 5 days a week over 5 weeks, total dose 45 Gy, 3D conformational technique) in combination with cetuximab (initial dose 400 mg/m^2 given one week before the beginning of radiation followed by 250 mg/m^2/week for 5 weeks) and two different doses of capecitabine for the duration of radiotherapy (including weekends), according to phase I methodology (650 mg/m^2 twice-daily, first dose level; 825 mg/m^2 twice-daily, second dose level). Dose-Limiting Toxicity (DLT) was defined according to Dunst (JCO 2002).
Results: Four and six patients (ECOG 0–1; median age: 62; transrectal ultrasound staging: T3N0: 5, T3N1:3, T4N0:2) were treated at the first and second dose levels of capecitabine, respectively. No DLTs occurred at either capecitabine dose. Radiotherapy was administered as planned to all patients. Adverse event profiles were consistent with the treatments used (grade 1/2 acne-like rash in all patients and grade 1/2 NCI-CTC diarrhea in 7 patients). Grade 3 NCI toxicities were observed in 5 patients (anal pain in 4 and dermatitis in 1). No grade 4 toxicity was recorded.
Conclusions: Preoperative radiotherapy in combination with capecitabine and cetuximab is feasible and well-tolerated for LARC. The recommended Doses for phase II evaluation are Capecitabine 825 mg/m^2 twice-daily without interruption during the duration of radiotherapy and Cetuximab at a loading dose of 400 mg/m^2 followed by 250 mg/m^2/week. The efficacy of this combination to downstage LARC is currently being investigated in a larger phase II study with a total planned accrual of 40 patients.

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Feasibility study of combined preoperative intensity-modulated radiation therapy (PIMRT) with concurrent capecitabine/oxaliplatin in patients with locally advanced rectal cancer (LARC)

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Background: Preoperative 5FU-based chemoradiation is the standard of care in LARC. New chemoradiation regimens based on Capecitabine and Oxaliplatin may enhance downstaging although acute effects may also be increased. IMRT may overcome this radiosensitizing phenomenon by decreasing the size of the PTV with a resultant reduction in the volume of several OAR's.
Material and methods: Patients (pts) with LARC received PIMRT *(step and shoot)* to 47.5 Gy in 19 treatments. Dose was prescribed at the Minimum Tumor Dose of the Gross Tumour Volume (GTV). Daily fractions of 2.5 Gy, 5 days a week were delivered. Capecitabine 825 mg/m^2 bid was given on the radiation days while Oxaliplatin was administered at a dose of 60 mg/m^2 on days 1, 5 and 15. Surgery was planned 4–6 weeks later. We used the RTOG criteria to evaluate acute toxicity. Pathologic response (PR) was analysed using the TNM staging and the scale proposed by the Memorial Sloan-Kettering Cancer Center: Grade 0 (no response), Grade 1 (1–33% PR), Grade 2 (34–66%), Grade 3 (67–95%), Grade 3+ (96–99%), Grade 4 (100%) (*Ruo et al. Ann Surg 2000)*.
Results: A total of 38 pts, 27 males and 11 females with a median age of 61 years, were treated between March 2003 and May 2005. All pt underwent endorectal ultrasound-based staging. Nine pts had T3N0 tumours (24%), 25 pts had T3N+ (66%), 2 pts had T4N0 (5%) and 2 pts had T4N+ (5%). Eighteen tumours (47%) were located in the distal rectum, 15 (39%) in middle rectum and 5 (13%) in the proximal third. Six pts received a lower PIMRT dose as part of an initial feasibility study. All pts except 8 (81%) completed the prescribed treatment; 6 pts did no receive the total dose of chemotherapy and 2 pts did no complete the prescribed radiation dose. Individual toxic events observed included: Diarrhea grade 1–2 (40%), Diarrhea grade 3 (8%), Tenesmus grade 1–2 (71%), Tenesmus grade 3 (13%), Dysuria grade 1–2 (16%) and Leukopenia grade 1–2 (2.5%). Overall, Grade 3 events were seen in 21% of the cases. Downstaging was observed in 20 pts (52%) with PR grade * 3+ in 45% of the specimens (Grade 4: 10%). In addition 21 of 25 initially N+ pts (84%) turned out to be pN0. The sphincter preservation rate for those pts with tumors located in the distal third of the rectum was 44%.
Conclusions: Concurrent Capecitabine/Oxaliplatin-based PIMRT (47.5 Gy/2.5 Gy/19 Rx) is feasible in pts with LARC. Grade 3 acute events are seen in 21% of the patients with an outstanding rate of PR grade * 3+.

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Acute appendicitis as a sign of a colorectal carcinoma

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Background: The concurrence of acute appendicitis and a colorectal carcinoma is well documented; suspicion is therefore raised of such a causal relationship in older patients. However, very few patients with colorectal cancer have had an appendicectomy within 3 years of the cancer diagnosis. There is no definite evidence that large bowel investigation is warranted following an appendicectomy for acute appendicitis in older patients. The aim of this study was to assess acute appendicitis in older patients as a sign of colorectal carcinoma and to investigate if there was a relationship between the two conditions.
Material and Methods: A 9 year retrospective review of all patients aged over 50 years taken to theatre with a presumed diagnosis of acute appendicitis. The study period was December 1995 to December 2004. Patient data was collected from theatre records, histology records and case notes. All inflamed appendices removed at colorectal cancer resections were not included.
Results: There were 1286 patients of all ages with histologically proven acute appendicitis. Of 167 patients older than 50 years taken to theatre, 114 (68%) had appendicitis whilst 53 (32%) had a normal appendix. Of the histologically positive cases, 54% were female and mean age was 65 (50–91) years. None had a synchronous colorectal cancer or other pathology at appendicectomy. Of the 114 positive cases, 31 (26%) had a subsequent large bowel investigation as an outpatient; most of these were requested by a consultant with a colorectal interest. No colorectal lesions were detected in these patients. Only 2/114 (1.8%) patients subsequently