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

R. Mass[1], S. Sarkar[1], S.N. Holden[1], H.I. Hurwitz[2]. [1]*Genentech Inc, South San Francisco, CA;* [2]*Duke University Medical Center, Durham, NC, USA*

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.

644 POSTER

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

S. Schildhauer[1], D. Pollmann[1], R. Geppert[1], K. Ocran[2], K.-D. Wernecke[3], K. Possinger[1], D. Lueftner[1]. [1]*Charite Campus Mitte, Medizinische Klinik / Onkologie, Berlin, Germany;* [2]*Charite Campus Mitte, Medizinische Klinik / Gastroenterologie, Berlin, Germany;* [3]*Charite Campus Mitte, Institut für Medizinische Biometrie, Berlin, Germany*

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.

645 POSTER

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

S. Aballea[1], M. Frick[2], R. Diel[3], S. Rosenfeld[2], E. Huppertz[2], M. Sievert[2], S. Jourdan[4], M. Drummond[5], M.C. Weinstein[6], P. Reichardt[7]. [1]*Innovus Research, High Wycombe, United Kingdom;* [2]*Sanofi-Aventis Germany, Berlin, Germany;* [3]*University Duesseldorf, Duesseldorf, Germany;* [4]*Sanofi-Aventis France, Paris, France;* [5]*University of York, York, United Kingdom;* [6]*Harvard University, Boston, USA;* [7]*Charite, Campus Virchow, Berlin, Germany*

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