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Results of a phase 2 study of HGS-ETR1, a fully human agonistic monoclonal antibody to TRAIL Receptor 1, in subjects with relapsed or refractory colorectal cancer (CRC)

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Background: HGS-ETR1 (TRM-1, mapatumumab) is an agonistic monoclonal antibody that targets TRAIL-R1 (DR4) and, upon binding to the receptor, causes apoptosis in target tissues. TRAIL-R1 is expressed in a broad range of solid tumors, including carcinomas of the colon. There is preclinical evidence of anti-tumor activity of HGS-ETR1 in vitro and in vivo. This study was designed to explore the therapeutic benefit of single agent HGS-ETR1 for the treatment of colorectal cancer.
Methods: 38 patients with relapsed or refractory Stage IIIB, IV or recurrent colorectal cancer were enrolled in a phase 2, open label, multi-center clinical trial. HGS-ETR1 was administered at 20 mg/kg every 14 days for cycles 1 and 2, and then 10 mg/kg in cycles 3–6, in the absence of disease progression. Patients with stable/responding disease were allowed to continue treatment at the same dose and schedule. The primary endpoint was tumor response evaluated with the RECIST criteria after every third treatment (approximately every 6 weeks). Safety and tolerability were assessed as secondary endpoints.
Results: 38 patients with a median age of 63 years (range 41–85 years) (21M: 17F) and an ECOG performance status 0–1 were entered on study. Patients had received up to 6 previous therapeutic regimens (median 2). Out of 38 patients evaluable for response, 12 had SD (32%), while 19 had progressive disease. The response status of 7 patients was still unknown at the time of this report. Patients with stable disease received from 3 to 7 cycles of HGS-ETR1. To date, there have been 7 reported SAEs, all unrelated to treatment and related to disease progression.
Conclusion: HGS-ETR1 can be safely administered to relapsed/refractory CRC patients. The best response observed to date in this heavily pre-treated population is stable disease. Patients tolerated therapy well with no patients discontinuing therapy due to toxicity related to drug. The study is still ongoing, updated efficacy and safety results will be presented at the meeting.

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

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Background: The MOSAIC trial demonstrated that oxaliplatin/5-FU/LV (FOLFOX4) as adjuvant treatment of stage 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 FOLFOX4 in this setting, from the perspective of the UK NHS.
Methods: We estimated the cost per quality-adjusted life-year (QALY) 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 UK general population, adjusting for age and gender. We assumed no relapse occurred beyond 5 years. We predicted OS beyond 4 years using the extrapolated DFS estimates and observed survival after relapse. Life-years accrued in both arms were assigned weights depending on occurrence of chemotherapy-related toxicities, disease status, and age to estimate QALYs. 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 bootstrapping approach.
Results: The extrapolated life expectancy of stage III patients on FOLFOX4 was 17.6 years compared to 16.2 years for patients on 5-FU/LV. The lifetime extrapolated incremental DFS between FOLFOX4 and 5-FU/LV was 1.99 years (95% confidence interval: 0.63 – 3.36). The number of QALYs, discounted at 3.5% per annum, increased by 0.68 (0.08–1.31) with oxaliplatin, from 8.58 with 5-FU/LV. The expected cost of treatment following relapse was under £11 000. Total discounted disease-related costs were £18 548 with oxaliplatin vs. £15 281 with 5-FU/LV over lifetime. The resulting incremental cost-effectiveness ratio for FOLFOX4 compared to 5-FU/LV was £4 805 (dominant – £45 658) per QALY gained.
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 discounted benefit of 0.68 QALY gained over lifetime in patients with stage III disease. If this benefit is confirmed, we estimate that FOLFOX4 would cost around £4,800 per QALY gained, which compares favourably with other accepted interventions in oncology.

References

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

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Association between carcinoembryonic antigen and vascular endothelial growth factor tumor tissue content of colorectal cancer

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We have recently demonstrated that tissue Vascular Endothelial Growth Factor (VEGF) content was higher in colorectal cancer (CRC) tissues compared to normal mucosa. Furthermore, tumor VEGF content was associated to clinicopathological variables and had an independent prognostic value in respect to overall survival. A significant correlation has been reported between preoperative serum VEGF and carcinoembryonic antigen (CEA) levels in colon cancer. Thus, we sought to investigate whether there is any relationship between VEGF and tumor markers tissue content in CRC. To this purpose, 69 patients with CRC were recruited (6 stage A, 37 stage B, 21 stage C and 5 stage D). No patient received neo-adjuvant chemotherapy or radiation therapy before surgery. No patient received antiangiogenic agents at any time. Surgery was carried out in all patients. Quantitative evaluation of VEGF, CEA, CA19.9 and CA72–4 content was performed on whole protein extracts obtained from biopsies of histologically confirmed neoplastic tissues and corresponding mucosa histologically confirmed as "normal". The results obtained showed the presence of a significant correlation between VEGF and CEA content of either tumor tissues ($\rho = 0.55$, $p < 0.0001$) or corresponding normal mucosa ($\rho = 0.34$, $p < 0.005$). No significant correlation was observed between VEGF and either CA 19.9 or CA 72–4 tissue content of sampled biopsies. Multivariate analyses including age, sex, grading, tumor size, lymph node involvement, and CEA, CA 19.9 and CA72–4 tissue content demonstrated that CEA levels were an independent predictor of VEGF tissue content either in CRC biopsies (regression coefficient=0.59, $p < 0.0001$) or normal mucosa (regression coefficient=0.28, $p < 0.05$). Nine patients had negative tumor CEA or VEGF content. All of them were alive and free of disease after a median follow-up of 5 years. Kaplan Meyer analysis of the remaining patients demonstrated that a positive tumor content of both CEA and VEGF had a negative prognostic value in respect to either relapse-free survival (log rank test: 2.94, $p = 0.003$) or overall survival (log rank test: 2.92, $p = 0.004$). In conclusion, tumor tissue VEGF and CEA content determination might add useful prognostic information in the management of patients with CRC. Furthermore, we hypothesize that CEA might be involved in the switch from non-invasive to invasive CRC cancer, as recently demonstrated for other CEA-related cell adhesion molecules.

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Long term results of a single institution prospective study of combined multimodality treatment for non-metastasized locally advanced or locally recurrent rectal cancer

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Purpose: Primary objective of this study was to develop a combined multimodality treatment for locally advanced or locally recurrent rectal

cancer. Secondary objective was to establish treatment related variables which correlate with oncological prognosis.
Methods: From 1994 until 2004, 203 patients with locally advanced and 117 patients with locally recurrent rectal cancer underwent multimodality treatment. All patients have been staged by MRI for the rectal cancer and by CT of the thorax and abdomen in order to rule out metastatic disease. In all primary cases the circumferential margin was involved or less than 2 mm free according to MRI. All pelvic locally recurrent cases were eligible. Multimodality treatment consisted of neoadjuvant radio-(chemo) therapy, resection, extended if necessary and Intraoperative Electron Radiotherapy (IOERT) at the area of risk. Concomitant chemotherapy was added to the radiotherapy since 1999.
Patients were referred from over forty different hospitals in the Netherlands. However, surgery and IOERT were performed in one institution.
Results: Five-year survival rate and local recurrence rate were 55% and 17% for locally advanced rectal cancer and 32% and 39% for locally recurrent rectal cancer respectively. After radical resection (R0) with negative circumferential margins, 5 year survival and local recurrence rate were 60% and 10% for locally advanced (n = 168) and 48% and 24% in locally recurrent cases (n = 68). Response to neoadjuvant treatment, and type of neoadjuvant treatment were statistically significant variables for obtaining radical resections. In primary advanced cases 30% showed poor response to neoadjuvant treatment, but were responsible for 86% of all irradical resections (30/35) In primary advanced rectal cancer cases R0 resection rate was 72% after neoajuvant radiotherapy only, and 89% after combined radiochemotherapy. In locally recurrent cases these figures were 56% and 68% respectively.
Conclusion: Combined multimodality treatment is effective in the treatment of locally advanced primary rectal cancer and can be used as salvage strategy for patients with locally recurrent rectal cancer. Treatment related factors: response to neoadjuvant treatment and the ability to perform a radical R0 resection strongly correspond with oncological outcome.

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Post-study treatment does not influence outcome in the X-ACT phase III trial of capecitabine (X) vs. bolus 5-FU/LV as adjuvant therapy for patients (pts) with Dukes' C colon cancer

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Background: The X-ACT trial evaluated adjuvant X vs. 5-FU/LV in pts with resected Dukes' C colon cancer. Between Nov 1998 and Nov 2001, 1987 pts were randomised to receive either oral X (1250 mg/m^2 bid d1–14, q3w) or i.v. bolus 5-FU/LV (Mayo Clinic regimen: LV 20 mg/m^2 + 5-FU 425 mg/m^2 d1–5, q4w) for 24 weeks. X was at least equivalent to 5-FU/LV in terms of disease-free survival (DFS; HR 0.87, 95% CI 0.75–1.00, $p < 0.0001$), with a strong trend towards superior DFS ($p = 0.053$). X significantly improved relapse-free survival (HR 0.86, 95% CI 0.74–0.99, $p = 0.041$), with a trend towards improved overall survival (HR 0.84, 95% CI 0.69–1.01, $p = 0.071$). The primary safety endpoint was met with fewer key grade 3/4 adverse events and later onset with X vs. 5-FU/LV ($p < 0.001$).
Materials and methods: In a separate analysis, we looked at post-study treatment in both arms of the X-ACT trial to determine whether there were any differences that could influence survival outcome.
Results: At the time of this analysis, 632 pts in the X and 579 in the 5-FU/LV arms are alive and disease-free, with 131 and 142 pts alive with relapse/new recurrence in the X and 5-FU/LV arms, respectively. Of the pts receiving post-study chemotherapy, 25 in the X and 10 in the 5-FU/LV arm received other adjuvant chemotherapy following randomisation into X-ACT either because they never received study treatment or at the investigator's discretion (after early termination of study treatment for any reason). In addition, 13 pts in the X and 16 pts in the 5-FU/LV arm received post-study chemotherapy for new occurrences of cancer other than colon cancer (breast, prostate, lung) prior to relapse. Pts meeting the entry criteria (free of disease at study entry and receiving $\geqslant$1 doses of study treatment) who were treated according to the protocol and experienced relapse formed the largest group receiving post-study chemotherapy. There were no major imbalances in post-study chemotherapy for metastatic disease (see table) or radiotherapy (6% in both arms).
Conclusions: These data suggest that there are no differences in post-study chemotherapy that could influence survival outcome in pts who received either X or 5-FU/LV as adjuvant therapy in the X-ACT trial. Efficacy, safety and pharmacoeconomic findings indicate that X should replace 5-FU/LV as adjuvant treatment for colon cancer.

% of pts receiving post-study chemotherapy for metastatic disease

	X (n = 372)	5-FU/LV (n = 404)
Irinotecan-based	39	35
5-FU-based	17	16
Oxaliplatin-based	32	29
X single agent	4	10
Other chemotherapy	9	6

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Arterial thromboembolic events in a pooled analysis of 5 randomized, controlled trials of bevacizumab with chemotherapy

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Background: Bevacizumab (Avastin^{TM}) is a monoclonal antibody to VEGF with demonstrated survival benefit when combined with chemotherapy in metastatic colorectal cancer (mCRC). Individual safety data from several randomized controlled trials suggested that adding bevacizumab to chemotherapy may increase the risk of arterial thromboembolic events. We conducted a pooled analysis to evaluate this potential safety signal.
Methods: Data from 1745 pts with metastatic carcinomas (breast, colorectal, and non-small-cell lung) pooled from 5 randomized controlled trials of bevacizumab with chemotherapy were analyzed to assess arterial thromboembolic event risk and identify predisposing factors in the context of overall clinical effect. Clinical parameters, including age, gender, development of proteinuria on study, and history of hypertension, diabetes, atherosclerosis, arterial thromboembolic events, venous thromboembolic events, and use of aspirin or a statin, were assessed for relationship to arterial thromboembolic event occurrence by univariate analysis and a Cox proportional hazards regression model.
Results: Within this pooled population, the addition of bevacizumab to chemotherapy increased the risk of arterial thromboembolic events compared to chemotherapy alone (3.8% vs 1.7%, $p < 0.01$ by Chi-square test). In addition to bevacizumab treatment, history of arterial thromboembolic events and age $\geqslant$65 years were identified as independent risk factors by multivariate analysis (hazard ratios of 1.9, 2.9, and 2.2 respectively).
Conclusion: The addition of bevacizumab to chemotherapy is associated with an increased risk of arterial thromboembolic events in patients with metastatic carcinoma, especially those $\geqslant$65 years old with a prior history of arterial thromboembolic events. The risk/benefit of bevacizumab in mCRC by arterial thromboembolic event-risk group will be presented.

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Initial safety findings from a phase III study of capecitabine (X) plus oxaliplatin (XELOX) vs. infusional 5-FU/LV plus oxaliplatin (FOLFOX-6) in first-line treatment of patients (pts) with metastatic colorectal cancer (MCRC)

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Background: The oral fluoropyrimidine X is replacing 5-FU/LV as the backbone of colorectal cancer therapy, in both the metastatic and adjuvant settings. The combination of X and 3-weekly oxaliplatin (XELOX) has demonstrated good efficacy and safety in phase II clinical trials in MCRC. We initiated a phase III trial to compare XELOX with FOLFOX-6 as first-line therapy in pts with MCRC. This abstract provides the initial safety findings from a planned interim analysis.