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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