in the remaining sporadic CRCs. No differences in disease-free survival (DFS) and overall survival (OS) were observed between MSI- and MSI+ patients with localization not including the rectum (median DFS: 18 and 19 months, respectively; median OS, 21 months in both groups), whereas a favourable prognostic value was found for rectal cancer patients with MSI+ (median DFS and OS: 30 and 34 months vs 22 and 25 months for MSI- cases, respectively). Preliminary data from IHC revealed a high concordance between down-regulation of MLH1 expression and presence of MSI+ phenotype. Significant CRC cases to be screened for mutations in mismatch repair genes have been thus identified.

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Clinical determinants of tumor response in patients with 5-FU based treatment for metastatic colorectal cancer. Results of a multivariate analysis of 3825 patients

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Purpose: To identify clinical prognostic factors predictive for response rate (RR) in previously untreated patients with metastatic colorectal cancer.

Methods: Source data of 3825 patients from 19 randomized trials have been analyzed using recursive partitioning and amalgamation (RECPAM) and cluster by response (CBR) methodology on a learning (LER) and validation (VAL) sample. Variables were grouped into laboratory (WBC, PLT, Hb, AP, LDH, Bilirubin, ALAT, ASAT, protein, albumin, CEA) or tumor burden (colon or rectal primary, grading, No of metastatic sites [NSites], presence of liver, lung, lymphnode or peritoneal metastases) or clinical parameters(ECOG, weight loss, tumor related symptoms). A minimum of 100 patients had to remain in any prognostic subgroup throughout the analysis. In the first step the analysis was performed in each group and the "winners" of each group then entered the final model.

Results: The final prediction model using CBR was as follows: good risk (n=956)(LER RR 29.9%; VAL RR 24.3%): ECOG(0/1) AND NSites(1 only) AND Hb (>11gpt/l); poor risk (n=734)(LER RR 15.8%; VAL RR 14.8%): all other patients. Using the RECPAM methodology good risk patients (LER RR27.8%; VAL 23.4%) had platelets ≤400x109/L AND Hb >11 gpt/l AND Nsites=1 AND no peritoneal mets AND ECOG=0,1; all other patients were poor risk patients (LER RR17.4%; VAL 14.5%). If treatment failure (prevention of early PD during chemotherapy) is the endpoint, patients with ECOG 0 or 1 AND Nsites=1 had a 71.2% chance of no early PD while all other patients had a 52.1% chance of no early PD.

Conclusions: Patients can be divided into at least 2 risk groups depending on initial performance status, WBC, number of metastatic sites and hemoglobin levels, parameters that were also identified as independent predictors for survival (ASCO 2000). Consistency between the two statistical methods is high. However, the prognostic power of these clinical parameters comes out to be considerably weaker for the prediction of response or prevention of early PD as compared to the prediction of survival. Other parameters like level of intratumoral thymidilate synthase may be more useful to predict response.

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Capecitabine in combination with oxaliplatin as first line therapy for patients (pts) with advanced or metastatic colorectal cancer (ACRC): preliminary results of an international multicenter phase II study

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Introduction: Xeloda (capecitabine) is a novel oral fluoropyrimidine, which is converted to 5-fluorouracil (5FU) at the tumour site by exploiting the higher activity of thymidine phosphorylase in malignant tissue. It has demonstrated superior activity and an improved safety profile compared with iv bolus 5-FU/leucovorin (LV) Mayo Clinic in two large phase III trials. Oxaliplatin combined with 5FU/LV is also a recognised first line therapy option for ACRC, with superior response rates and time to progression compared with 5FU/LV alone in phase III trials.

Methods: Following a phase I study, the current phase II trial evaluated the efficacy and safety of oral capecitabine (1000 mg/m2 twice daily d1-14, q3 weeks) and intravenous oxaliplatin (130 mg/m2 d1, q3 weeks) as first line therapy for pts with ACRC.

Patient characteristics: At present enrolment is completed with 96 pts. For this preliminary report pts enrolled during the first 4 months of the study were included: 37 are assessable for safety and 34 for efficacy. The median number of treatment cycles per pt was 6 (1-10). Twenty-six men and 11 women, with a median age of 65 years (48-79 years) and a median Karnofsky Performance Status of 100 (80-100) were included. 28 (76%) pts had liver metastases.

Safety: Grade 3/4 adverse reactions reported in more than one pt were vomiting (14%), nausea (11%), diarrhea (8%), neutropenia (8%) and thrombocytopenia (5%). Of note, no pts had grade 3 hand-foot syndrome (24% grade 2) or grade 3/4 peripheral neuropathy (8% grade 2). There were two cases of laryngo-pharyngeal dysesthesia (grades 2 and 3). Six (16%) pts withdrew from study due to thrombocytopenia, asthenia, hemiparesis, diarrhea, lethargy, flushing. The most common grade 3/4 laboratory abnormality was increased bilirubin, found in 19% of pts, which was not associated with grade 3/4 elevated liver enzymes. Elevated bilirubin is a known phenomenon with oral fluoropyrimidines. One death was attributed to study treatment: respiratory failure in a pt with pre-existing pulmonary fibrosis.

Efficacy: The objective response rate was 50%, including 2 complete and 15 partial responses (3 PR not yet confirmed). A further 10 pts (33%) had stable disease. Of 11 pts who had received prior adjuvant fluoropyrimidine treatment, 6 pts achieved a PR (55%).

Conclusion: These data indicate that the capecitabine and oxaliplatin combination is highly active and has an acceptable safety profile as first line therapy in ACRC.

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Marked differences in tumour-associated protein expression and genetic stability between proximal and distal colon tumours

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Purpose: There is increasing evidence that proximal and distal colon tumours comprise distinct diseases, which may impact on the clinical outcomes of colon cancer patients. The aim of this study was to characterise phenotypic and genomic differences between proximal and distal colon tumours.

Methods: IHC was carried out on 189 colon tumours (n=90 proximal and n=99 distal tumours), to evaluate the expression of the following proteins: beta-catenin, cyclin D1, pRb, p53, p21, p27, p16, PCNA and EGFR. In addition, CGH was used to evaluate genetic aberrations in a subset of 25 samples (n=9 proximal and n=16 distal tumours). Analysis of protein expression with respect to tumour site was carried out using the chi-squared test, while patient survival was tested using Kaplan-Meier survival plots and analysed using the log rank test.

Results: Several of the proteins evaluated by IHC demonstrated distinct differences in expression between proximal and distal colon tumours. Nuclear accumulation of beta-catenin was markedly less frequent in proximal tumours compared to distal lesions (P=0.002), as was aberrant expression of p53 (P=0.028). Conversely, p21 protein was more commonly expressed in proximal tumours (P=0.018). While EGFR expression did not vary significantly between the tumour sites, expression was associated with patient survival in proximal tumours (P=0.018), but not in distal lesions (P=0.807). Further disparity was observed between proximal and distal tumours using CGH, where the total number of genetic aberrations in proximal tumours (n=8.7) was notably higher than in distal lesions (n=4.8).

Conclusion: Marked differences in the expression of tumour-associated proteins, and also in the level of genomic aberration, have been demonstrated between proximal and distal colon tumours. These dissimilarities may have an effect on the clinical outcomes of colon cancer, including patient survival. Elucidating such differences might therefore assist in selecting the treatment options most likely to be effective.