34-month RFS was 95%. All pts achieving a TRG1, and all but one with TRG2 (pCRM +ve), were recurrence-free.
Conclusions: These data confirm the feasibility and activity of the whole treatment. A slight reduction of FU dosage appeared to improve the safety of this combination. Currently, we are now evaluating the addition of bevacizumab, 5 mg/kg every 2 weeks, before and during this concurrent

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Induction of dihydropyrimidine dehydrogenase expression by Mitomycin C in colorectal cancer

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Background: Since thymidine phosphorylase (TP) is an essential enzyme for the activation of capecitabine to 5-fluorouracil (5-FU) in tumors, TP up-regulators should enhance the efficacy of capecitabine. Dihydropyrimidine dehydrogenase (DPD), on the other hand, is considered to be a key enzyme in the catabolism of 5-FU, and its high expression in a tumor is thought to reduce the efficacy of 5-FU against tumors. The aim of this study was to confirm whether or not mitomycin C (MMC) is a TP and/or DPD regulator.
Materials and Methods: Biopsy specimens were obtained from 62 colorectal cancer patients preoperatively by colonoscopy. After a biopsy, 33 patients received neoadjuvant chemotherapy with MMC and underwent operations after 1−13 days. Using biopsy and operative specimens, TP and DPD levels in the tumors were examined. Patients were divided into three groups; an MMC(−) group (no MMC), a Short group (operation within four days after MMC) and a Long group (operation over six days after MMC).
Results: In the MMC(−) and Short groups, no significant differences in DPD levels before and after MMC were observed. In the Long group, on the other hand, DPD levels were elevated ($p = 0.026$). As for TP, MMC did not raise the levels of TP in the MMC(−) and Short groups, but it tended to do so in the Long group ($p = 0.13$).
Conclusions: Although MMC appears to be a TP up-regulator, it is also a DPD up-regulator at appropriate intervals.

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A Swiss multicentre phase II study of capecitabine plus oxaliplatin (CAPOX) in combination with preoperative pelvic radiotherapy in patients (pts) with locally advanced rectal cancer

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Background: This study evaluated the addition of capecitabine and oxaliplatin (CAPOX) to preoperative radiotherapy (RT) in patients with locally advanced rectal cancer (LARC).
Materials and Methods: Patients (pts) with T3/T4 rectal adenocarcinoma with or without nodal involvement staged by endorectal ultrasound were recruited. Treatment consisted of a full dose cycle with CAPOX (capecitabine 1000 mg/m^2 bid on days 1–14 and oxaliplatin 130 mg/m^2/d on day 1), followed by RT as 25 daily fractions of 1.8 Gy on 5 consecutive weeks in combination with capecitabine 825 mg/m^2 bid on days 22–35 and 43–56 and oxaliplatin 50 mg/m^2/d on days 22, 29, 43 and 50. Surgery was scheduled 5 weeks after completion of CAPOX-RT. Primary endpoint was pathological complete tumour response (pCR) prospectively defined as grade 3 or 4 in the histological grading of regression according to Dworak classification (DC). Secondary endpoints were rate of sphincter preservation, R0 resection in pts with T4 tumours, downstaging, pathological incomplete tumour response rate and safety. Second-opinion pathology review was performed in all tumours categorised as DC grade 2 or 3.
Results: 60 pts were enrolled from 6 cancer centres. Median tumour size was 50 mm. Nodal infiltration was diagnosed in 47 pts. Tumour location (from anal verge): $\leqslant$5 cm in 21 pts, 5–10 cm 22 pts, >10 cm 17 pts. 58 pts received CAPOX-RT and underwent surgery (49 TME, 9 abdominoperineal resection), 1 pt withdrew consent and refused further treatment, and 1 died during neoadjuvant CAPOX. R0 resection was achieved in 57 pts, including all 5 pts with T4 tumours. The pCR rate was 23% (95% CI, 13–36; DC 3: 7 pts, DC 4: 7 pts). Sphincter preservation was achieved in 84% of pts. Tumour downstaging (T and/or N) was observed in 65% of pts. Pathological incomplete response (DC 0/1/2) was observed in 1/20/23 pts. Main grade 3 adverse events were: diarrhoea 20%; thrombosis 3%; nausea, vomiting, proctitis, fatigue, hand–foot syndrome 2% each. No grade 3/4 haematological adverse events, except lymphocytopenia (43%), were observed.
Conclusions: Preoperative combined treatment with CAPOX and RT is feasible and resulted in encouraging high rates of pCR, R0 resection, sphincter preservation, and tumour downstaging in this group of pts with LARC.

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Randomized strategical trial of chemotherapy in metastatic colorectal cancer (FFCD 2000−05): preliminary results

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Background: The survival benefit of using a combination therapy instead of keeping it for a second line (L2) has not been demonstrated in metastatic colorectal cancer. The purpose of this trial was to compare the efficacy of simplified LV5FU2 (s) followed by FOLFOX6 (arm A) to FOLFOX6 followed by FOLFIRI (arm B) on progression-free survival after two lines of chemotherapy. We present here preliminary results relating to toxicity, observance and overall survival.
Materials and Methods: Inclusion criteria: a) non resectable metastases of histologically proven colorectal adenocarcinoma, b) evaluable disease (WHO criteria), c) absence of previous chemotherapy other than adjuvant. Treatment was as follows: LV5FU2s = at day 1, folinic acid 400 mg/m^2, 5-FU bolus 400 mg/m^2 and continuous infusion over 46 hours 2400 mg/m^2/2 weeks; FOLFOX6 = LV5FU2s + oxaliplatin 100 mg/m^2 at day 1; FOLFIRI = LV5FU2s + irinotecan 180 mg/m^2 at day 1.
Results: 410 pts out of 570 initially planned (early stopping due to slow accrual and new treatments) were included from 02/2002 to 02/2006 (205 in each arm). Median follow-up was 25 months. The median number (range) of cycles (28 days) in first line (L1) was respectively 5 (1−24) and 6 (1−24) in the arms A and B ($p = 0.01$), and for L2 (152 and 144 pts in the arms A/B): 5 (1−17) and 3 (1−33) (NS). In the arms A and B, 74% and 70% of pts had L2. L1 was stopped for toxicity for 1% and 16% of the pts in arms A and B ($p < 0.0001$); L2 respectively for 15% and 2% pts ($p < 0.0001$). The percentages of pts presenting at least a grade 3−4 hematologic toxicity (mainly neutropenia) by arm were: 6% versus 37% ($p < 0.0001$) for L1 and 30% versus 27% (NS) for L2; grade 3−4 non hematological toxicity (grade 2−4 neurotoxicity): 26% (1%) versus 56% (64%)($p < 0.0001$; $p < 0.0001$) for L1 and 54% (60%) versus 46% (40%) of the pts for L2 (NS; $p < 0.01$). No toxic death was observed in the arm A against 5 in the arm B: 3 in L1 and 2 in L2. Overall survival medians were 17 and 16 months in arms A/B (logrank $p = 0.64$) (preliminary results, 291 observed deaths).
Conclusions: This trial does not show any substantial difference in treatment duration and overall survival between both arms and shows a more important toxicity in the arm with first line combined chemotherapy.

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Significance of polymorphisms in biotransformation enzymes for colorectal carcinogenesis

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Background: Biotransformation enzymes play important role in metabolism of xenobiotics. Genetic polymorphisms in biotransformation enzymes may result in variations in detoxification capacity. Interaction