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580O MFOLFOX6 + CEDIRANIB VS MFOLFOX6 + BEVACIZUMAB IN PREVIOUSLY UNTREATED METASTATIC COLORECTAL CANCER (MCRC): A RANDOMIZED, DOUBLE-BLIND, PHASE II/III STUDY (HORIZON III)

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Background: Cediranib is a highly potent VEGF signalling inhibitor with activity against all three VEGF receptors. Bevacizumab (bev) is an anti-VEGF-A monoclonal antibody with known clinical benefit in mCRC. HORIZON III compares mFOLFOX6 + cediranib with mFOLFOX6 + bev in patients (pts) with previously untreated mCRC.

Methods: This study had an adaptive Phase II/III design. Eligible pts were randomized 1:1:1 to receive mFOLFOX6 q2w with cediranib (20 or 30 mg/day) or bev (5 mg/kg iv q2w). An independent end of Phase II analysis showed that cediranib 20 mg met all of the predefined criteria for study continuation; subsequent pts were randomized 1:1 to mFOLFOX6 with cediranib 20 mg or bev. The primary objective was to compare progression-free survival (PFS; predefined non-inferiority limit upper 95% CI for hazard ratio [HR] <1.2). Secondary endpoints included overall survival (OS), objective response rate (ORR), safety and tolerability.

Results: Between Aug 2006 and Jan 2009, 1422 pts received mFOLFOX6 with cediranib 20 mg (n=709) or bev (n=713). Baseline characteristics were similar in both arms. At data cut-off (Nov 2009), 65% pts had events for the primary PFS analysis and 34% had died. There was no significant difference between the cediranib and bev arms for PFS (HR=1.10, 95% CI 0.97, 1.25; P=0.119; median=9.9 vs 10.3 months), preliminary OS (HR=0.94, 95% CI 0.79, 1.12; P=0.546) or ORR (46.3% vs 47.3%). Common adverse events (AEs) of any grade (>20% per arm with >5% higher incidence in the cediranib arm) included diarrhoea, neutropenia, hypertension, stomatitis, thrombocytopenia and abdominal pain. There was a difference in chemotherapy dosing between the arms; patients in the cediranib arm received fewer cycles (median 10 vs 12) and a lower dose intensity after 3 months from randomization.

Conclusions: There was no statistically significant difference in PFS, OS or ORR for cediranib + mFOLFOX6 vs bev + mFOLFOX6; however, the predefined boundary for PFS non-inferiority was not met. The safety profile of cediranib was consistent with previous studies, although there was a higher incidence of common AEs with cediranib + mFOLFOX6 than bev + mFOLFOX6.

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581PD TRIAL PARTICIPATION IN A MULTICENTRE PHASE III TRIAL (CAIRO) IN ADVANCED COLORECTAL CANCER (ACC) PATIENTS (PTS) IN THE NETHERLANDS, AND A COMPARISON OF OUTCOME BETWEEN TRIAL AND NON-TRIAL PTS

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Background: There is general consensus that progress in cancer research is hampered by a low accrual rate of pts in clinical trials. Trial participation of pts has been estimated between 2-4%, with in some studies 10-14% for potentially eligible pts. Efforts for improvement are often accompanied by the argument that treatment within a clinical trial may result in a better outcome compared with off-study treatment.

Methods: As of January 2003, 820 ACC pts were included within 2 years in the CAIRO trial of the Dutch Colorectal Cancer Group. This trial investigated the optimal use of approved cytotoxic drugs, with entry criteria that also apply to the use of these drugs in general practice. Trial participation was compared with data from the Netherlands Cancer Registry (NCR), which registers all cancer pts at primary diagnosis. Therefore metastatic pts are only registered when they present with stage IV. Non-trial pts who were registered by NCR during the trial accrual period in 29 randomly selected hospitals were checked for CAIRO eligibility criteria, and outcome of non-trial pts who fulfilled these criteria was compared with trial pts.

Results: Of the 803 eligible CAIRO pts, 400 had stage IV disease at diagnosis. During the accrual period, NCR registered 4201 stage IV ACC pts of whom 1962 received chemotherapy. Thus, trial participation of stage IV ACC pts was 20%. 219 out of 433 NCR-identified pts that received chemotherapy in the selected 29 hospitals would have been eligible but were not included in the CAIRO study and had comparable baseline characteristics compared with trial pts. Trial participation in these 29 hospitals was 39%. Overall survival of eligible non-trial pts was comparable to trial pts (HR 0.99, p=0.7). Non-eligible non-trial pts had a significantly worse outcome.

Conclusion: In this retrospective analysis, using a large multicentre chemotherapy trial in ACC as a reference, we demonstrate that a trial participation of 39% is feasible. Our results also indicate that trial results may be extrapolated to general practice provided that eligibility criteria are observed. These results may serve as a landmark for future studies.

Disclosure: All authors have declared no conflicts of interest.

582PD CETUXIMAB PLUS XELIRI VERSUS CETUXIMAB PLUS XELOX AS FIRST-LINE TREATMENT FOR PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC): ANALYSIS OF THE RANDOMIZED TRIAL OF THE GERMAN AIO CRC STUDY GROUP: KRK-0204

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Introduction: Cetuximab combined with 5-fluorouracil/folinic acid plus irinotecan or oxaliplatin has shown activity in the treatment of mCRC. This randomized phase II trial investigated the efficacy and safety of the epidermal growth factor receptor antibody cetuximab combined with the oral fluoropyrimidine capecitabine plus irinotecan (XELIRI) or oxaliplatin (XELOX) in the first-line treatment of mCRC.

Methods: A total of 185 mCRC patients were randomized to cetuximab (400mg/m^2 day 1, followed by 250mg/m^2 weekly) plus XELIRI (irinotecan 200mg/m^2, day 1; capecitabine 800mg/m^2 twice daily days 1-14, every 3 weeks; 20% dose reduction of both agents for patients older than 65 years) or cetuximab plus XELOX (oxaliplatin 130mg/m^2 day 1; capecitabine 1000mg/m^2 twice daily days 1-14, every three weeks). The primary study endpoint was objective response rate (ORR). KRAS (wild-type or mutant) on codons 12/13/61/146 and BRAF mutation status was determined using a mutation-specific quantitative PCR-based assay.

Results: In the intention-to-treat patient population (n=177), ORR was 47.2% (95% CI: 36.5-58.1) versus 47.7% (95% CI: 37-58.7) and the disease control rate 74.2% versus 77.3% for cetuximab plus XELIRI versus cetuximab plus XELOX. Time to progression and overall survival were 6.4 and 21.1 months for cetuximab and XELIRI compared to 8.2 and 25.5 months for cetuximab and XELOX. Determination of KRAS status was possible

in 78.5% of patients (n=139). 61.2% of those patients showed a KRAS wild-type, and 38.8% a mutant KRAS status. No differences regarding ORR, DCR, OS or PFS could be observed in KRAS wild-type compared to KRAS mutated patients. Both study treatments had manageable tolerability profiles and were safe. The most common grade 3/4 toxicities in the cetuximab plus XELIRI arm versus cetuximab plus XELOX arm were diarrhea (15.7% versus 19.3%), cetuximab-induced exanthema (13.5% versus 20.5%), and sensory neurotoxicity (1.1% versus 14.8%).

Conclusion: This randomized trial demonstrates the efficacy and tolerability of cetuximab combined with XELIRI or XELOX for the first-line treatment of patients with mCRC, while KRAS mutation status was not predictive of treatment outcome.

Disclosure: All authors have declared no conflicts of interest.

583PD EFFICACY AND SAFETY OF SECOND-LINE TREATMENT WITH PANITUMUMAB PLUS IRINOTECAN, BOTH GIVEN EVERY THREE WEEKS (Q3W), IN PATIENTS (PTS) WITH WILD-TYPE (WT) K-RAS METASTATIC COLORECTAL CANCER (MCRC): A STUDY FROM THE SPANISH COOPERATIVE GROUP FOR THE TREATMENT OF DIGESTIVE TUMORS (TTD)

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Background: Panitumumab (Pmab) has demonstrated efficacy and a manageable safety profile either in monotherapy or in combination with chemotherapy for the treatment of mCRC in pts with WT K-RAS tumors. This phase II, multicenter, single-arm study (clinicaltrials.gov identifier NCT00475293) evaluates the efficacy and safety of Pmab plus Irinotecan (Iri) given Q3W as second-line treatment for mCRC pts. K-RAS status as a negative predictive marker for Pmab efficacy was not established by the time the trial was planned and started. A protocol amendment was performed to recruit only WT K-RAS tumors when 44 pts were already included

Methods: Eligible pts had to have confirmed mCRC with measurable disease, ECOG score 0-2 and older than 18 years. Pmab 9 mg/kg plus Iri 350 mg/m^2 (300 mg/m^2 in pts >70 years-old or ECOG 2) were administered Q3W until progressive disease (PD) or unacceptable toxicity. Tumor assessments (modified RECIST criteria) were performed Q9W until PD. The primary endpoint was objective response rate (ORR) and secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and adverse events (AEs)

Results: A total of 85 pts have been enrolled in the study. This analysis was performed on an intention-to-treat basis in the subset of pts with WT K-RAS tumour (53 pts) Pts characteristics: 66% men, median age 67 years (range 37-83), and 90.6% ECOG 0-1. ORR was 22.6% (95% confidence interval [CI] 12.3-36.2) and median time duration of response was 4.3 months (range 2.5-15.0). DCR was 64.1% (95%CI 49.8-76.9). Median PFS and OS were 4.5 (95%CI 2.1–8.4) and 15.1 months (95%CI 4.5–22.5) respectively. Most common grade 3/4 related AEs were diarrhoea (35.8%), acne-like rash (32.1%), asthenia (18.9%) and neutropenia (13.2%). Two treatment related deaths were reported (gastric ileus and sudden death)

Conclusions: From our knowledge this is the first time to show the promising activity and safety profile of the Pmab and Iri combination both administered Q3W as second-line therapy in WT K-RAS mCRC pts.

Disclosure: E. Aranda: Amgen, Consultant or advisory role.

All other authors have declared no conflicts of interest.

584PD IMPACT OF KRAS STATUS ON SURVIVAL IN PATIENTS (PTS.) WITH METASTATIC COLORECTAL CANCER (MCRC) UNDERGOING BEVACIZUMAB (BEV) CONTAINING CHEMOTHERAPY REGIMEN– ANALYSIS OF THE AIO COLORECTAL CANCER STUDY GROUP

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Introduction: The predictive value of KRAS mutation status in pts. with mCRC undergoing anti-EGFR-antibody treatment is well described. However, its prognostic value under bevacizumab containing therapy is less clear (Ince, JNCI 2005; Hurwitz, The Oncologist 2009). We therefore analyzed the correlation of KRAS mutations with survival in pts. with mCRC from the randomized AIO KRK 0604 phase 2 trial for both treatment arms, capox-bevacizumab and capiri-bevacizumab.

Methods: Clinical results of the trial have been reported elsewhere (Schmiegel et al., ASCO 2007). For KRAS mutation status, formalin fixed paraffin embedded tumor tissue (FFPE-TT) from pts. was collected after obtaining informed consent and approval from the local ethics review board. Samples were macrodissected and DNA was extracted using the QIAmp DNA Mini kit (Qiagen, Hilden, Germany). Real-Time PCR amplification for the seven most common KRAS mutations in codons 12, 13 and 61 was performed using commercially available kits from DxS Ltd. (Manchester, UK) Colorectal cancer cell lines with known mutations in KRAS served as controls.

Results: FFPE tumor tissue from 146 out of 255 randomized pts of the trial was collected (57,2%). KRAS analysis was successful in 142 pts (97,2%). In 100 pts (70.4%) no KRAS mutation was detectable (KRAS Wild-Type; WT) while in 42 pts (29.5%) we found a mutation (KRAS mutated; MT). Progression free survival (PFS) was 10.8 months (mos.) in WT pts and 9.3mos. in MT pts. (p=0.32). OS was 28mos. in WT pts. and 21mos. in MT pts. (p=0.19). For the treatment arms, PFS in the capox-bevacizumab group was 10.4mos. for WT and 8mos. for MT pts. (p=0.12) and OS in the capox-bevacizumab group was 26.7 mos. and 19.3 mos. for WT and MT, respectively (p=0.067). In the capiri-bevacizumab treated group, PFS in WT and MT was 12.1mos. and 12.7mos., respectively (p=0.89) while OS in WT and MT was 28 mos. and 25mos. in the capiri-bevacizumab group, respectively (p=0,88).

Discussion: We found no significant difference in PFS or OS between WT and MT KRAS mCRC pts. for the whole cohort. The trend towards improved OS for the WT group may be explained with the number of EGFR based regimen in subsequent treatment lines. For the capiri-bevacizumab regimen, no difference was observed between WT and MT pts.. These findings are in contrast to the reports from the IFL-bevacizumab regimen (Ince, Natl. J Cancer Inst 2005). For the capox-bevacizumab group, a trend in worse PFS and OS for MT KRAS patients was seen. However, the relative small sample size limits for definitive conclusions, and all needs to be confirmed in larger series.

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585PD THE MULTI-TARGETED KINASE INHIBITOR AEE788 EXERTS ANTI-PROLIFERATIVE EFFECTS IN BRAF MUTATED COLORECTAL CANCER CELLS

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Background/Aims: EGFR-KRAS-BRAF signaling system is essential for the establishment and maintenance of cancer cells. BRAF is a downstream molecule from KRAS in a signaling pathway involved in cell proliferation and survival. Both KRAS and BRAF are prone to mutations in sporadic colorectal carcinomas. Advanced colorectal cancer patients with tumours harboring a mutation in the KRAS or BRAF genes do not derive benefit from the administration of epidermal growth factor receptor (EGFR)-directed monoclonal antibodies, such as cetuximab or panitumumab. Therefore, other targeted therapies are needed. AEE788 is a novel synthesized oral small-molecule multi-targeted kinase inhibitor with potent inhibitory activity against both EGFR and vascular endothelial growth factor receptor (VEGFR). The aim of this study was to determine the efficacy of AEE788 to inhibit cell proliferation in colorectal cancer cells with different RAS/BRAF mutational status, and to explore the involved mechanisms.

Methodology: The human colorectal cancer cell lines SW48 (KRAS/BRAF non-mutated), Caco-2 (BRAF V600E) and HCT-116 (KRAS G13D) were treated with AEE788, in the presence or the absence of EGF or VEGF. Cell proliferation was measured using a XTT assay. The expression and phosphorylation levels of EGFR, VEGFR, Akt and Erk1/2 were determined by western-blot using the corresponding specific antibodies.

Results: In all the three cell lines AEE788 effectively inhibited the phosphorylation of EGFR induced by EGF. In addition, AEE788 was capable to reduce the EGF-dependent cell proliferation of SW48 and Caco-2 cells, but not of HCT-116 cells. Significantly,

AEE788 reduced the VEGF-dependent cell proliferation of Caco-2, but not of SWS48 or HCT-116 cells. These antiproliferative effects were associated to reduced activation of the EGFR/VEGFR downstream kinases Akt and ERK1/2 only in Caco-2 cells.

Conclusions: AEE788 exerts anti-proliferative effects in BRAF mutated colorectal cancer cells, by inhibiting both EGF- and VEGF-induced cell proliferation. Our results support that AEE788 may be effective in the management of colorectal cancer in a non-mutated KRAS setting, independently of BRAF mutational status.

Disclosure: All authors have declared no conflicts of interest.

586PD HIGH THROUGHPUT SOMATIC PROFILING OF THE RAS-RAF-MAP AND PI3K-PTEN-AKT PATHWAYS IN ADVANCED COLORECTAL CANCER AND CORRELATIONS WITH RESPONSE TO CETUXIMAB

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Response to treatment of colorectal cancer (CRC) is influenced by each tumour's somatic genetic profile. For example, cetuximab, a monoclonal antibody against EGFR, has proven efficacy in K-ras wild-type tumours but is in general ineffective against K-ras mutant tumours. We developed Pyrosequencing and Sequenom assays for somatic profiling of codons 12, 13 and 61 of K-ras and codon 600 of B-raf. Both assays detected low levels of mutant alleles (~4%), had 99.12% (8642/8719) and 98.14% (1319/1344) genotype concordance for K-ras and B-raf mutations, respectively and high genotype success rates (96.7% for Sequenom vs. 92.5% for Pyrosequencing). Three multiplex Sequenom assays allowed high-throughput screening for additional somatic mutations within the Ras-Raf-MAP kinase and PI3K-PTEN-Akt pathways (codons 594 of B-raf, 12 of N-ras and 542, 545, 546, 1047 of PIK3CA). In total, we screened 1,976 CRCs from patients on the COIN trial (ISRCTN27286448) and found thirteen different K-ras mutations in a total of 42.27% of CRCs, two B-raf mutations in 9.01% of CRCs, four N-ras mutations in 3.56% of CRCs and five PIK3CA mutations in 12.81% of CRCs. We have previously shown that the addition of cetuximab improves progression free survival (PFS) in patients with K-ras, B-raf and N-ras wild-type tumours, where the partner chemotherapy was OxMdG and when disease extent was limited to 0 or 1 metastatic sites (HR=0.73, p=0.04). Here, we analysed individual somatic mutations with respect to response. We observed some interesting differences including a trend toward favourable response (PFS) to cetuximab in patients with K-ras G12V CRCs (HR=0.92, n=141 patients; and HR=0.78 for those 55 patients treated with OxMdG). However, the individual groups did not reach statistical significance and therefore warrant further investigation in additional cohorts. In collaboration with the COIN Collaborative Group.

Disclosure: All authors have declared no conflicts of interest.

587PD ONCOLOGIC AND FUNCTIONAL OUTCOMES AFTER PREOPERATIVE CHEMORADIOTHERAPY FOLLOWED BY INTERSPHINCTERIC RESECTION FOR VERY LOW RECTAL CANCER

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Purpose: We conducted a prospective single-institutional study of preoperative chemoradiotherapy (CRT) followed by intersphincteric resection (ISR), and compared the oncologic and functional outcomes with those treated by ISR alone for very low rectal cancer.

Methods: December1999 and May 2007, a total of 144 patients with very low rectal cancer have been treated using ISR. All patients have competed their three-year follow-ups. Of these patients, one group of 46 had preoperative CRT from 2001 to 2005, followed by the ISR procedure. This groups regimen of preoperative CRT was a total dose of 45Gy and a continuous infusion of 5FU with a total dose of 2500mg per week, and resection was performed two weeks later. The second group of 98 patients were treated with ISR alone. We compared the disease-free survival rates and local recurrence ratio among the two groups, and evaluated the effect on anal functionsl by preoperative CRT plus ISR. The risk factors for local recurrence were also analyzed.

Results: There were no differences in gender, age, operative procedures, c-Stage and follow-up terms among the two groups. The 3-yr DFS was not different between two groups (CRT+/-:72%/69%, P=0.55). There was no significant difference in the 3-yr cumulative incidence local recurrence (8%/16%, P=0.19). In the univariate analysis, poor anal function was significantly associated with male and with preoperative CRT. In the multivariate analysis, preoperative CRT was the only independent factor associated with poor anal function after ISR (odd's ratio=8.2; 95%CI: 2.5-26.5). Radial margin of less than 1mm was identified to be the independent risk factor for local recurrence after ISR. In patients with radial margin of less than 1mm, local recurrence rate after preoperative CRT+ISR showed 16% and that after ISR alone showed 41%.

Conclusions: When ISR was performed for very low rectal cancer, an addition of preoperative CRT did not clearly lead a significant reduction of local recurrence. However, preoperative CRT was found to be the factor most strongly associated with poor anal function. When performing ISR, preoperative CRT should be added only in patients who had a high risks of local recurrence.

Disclosure: All authors have declared no conflicts of interest.

588PD TRANS-ARTERIAL CHEMOEMBOLIZATION OF METASTATIC COLORECTAL CARCINOMA (MCRC) TO THE LIVER ADOPTING POLYVINYL ALCOHOL MICROSPHERES (PAM) LOADED WITH IRINOTECAN COMPARED WITH FOLFIRI (CT): EVALUATION AT TWO YEARS OF A PHASE III CLINICAL TRIAL.

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Introduction: MCRC is one of the leading causes of cancer-related death. The systemic spread of this disease occurs to the liver (LM). Patients with LM have a poor prognosis with the 5-yr survival of 25% after resection; for not operable LM survival is 5%. Surgery is feasible in a minority of patients. Most of them receive palliative chemotherapy. The PAM are new embolic materials and shown to actively sequester IRI from solution. DEBIRI (D) is TACE with PAM IRI preloaded occluding the LM feeding arteries. It is a safe procedure (ASCO GI abs 480,Jan 2008). FOLFIRI is active for the treatment of MCRC. We planned this phase III study to assess survival as primary endpoint with the goal of increasing median survival (MS) by 40% at 2-y (HR=0.72). QoL, responses, progression free survival (PFS) and safety were secondary endpoints. MS results were adjusted for this 24 month analysis.

Methods: Between December 2006 and December 2008, 74 pts were randomized, 36 patients to D (DC Beads loaded with IRI 200 mgr total dose) and 39 to CT (IRI 180 mg/ m^2 on day 1 with LV 100 mg/m^2 administered as a 2-hour infusion before FU 400 mg/ m^2 administered as an intravenous bolus injection, and FU 600 mg/m^2 as a 22-hour infusion on days 1 and 2). Four CT patients refused, and one D patient had early progression. 72 cycles of D were administered in 35 pts, with a relative dose intensity of 99%, and 292 CT cycles were delivered to 35 pts with a relative dose intensity of 90%.

Results: At a median follow up of 24 months (8-36) we reported : Med Surv=38%(D) vs 18% (CT), Response Rate=70% vs 20%, acute toxicity= 70% vs 20%, late Toxicity 20% vs 80%, QoL improvement=65% vs 25%, Costs for each pt: 4,500 vs 10,250 euro .

Conclusions: D increased the 24-Month Med Surv difference of 20% compared with CT. D improved responses, Performance Status and reduced costs. D reported higher immediate toxicity, mainly fever, abdominal pain than CT. Late toxicity, mainly leukopenia, anemia, diarrhoea, asthenia and alopecia, was more common in CT. We conclude that D, even if it does not reach the goal of increasing MS by 40% at 2-y compared with CT, is effective and feasible.

Disclosure: All authors have declared no conflicts of interest.

589P INTEGRATIVE EVALUATION OF EGFR DOWNSTREAM SIGNALLING FUNCTIONALITY TO PREDICT RESPONSE TO ANTI-EGFR MONOCLONAL ANTIBODIES IN KRAS WILD-TYPE MCRC

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Background: KRAS mutational status was shown to be a highly predictive marker for tumour response to anti-EGFR monoclonal antibodies (cetuximab, panitumumab) in metastatic colorectal cancer (mCRC). However, KRAS status has a poor negative predictive value (NPV), which clearly suggests that additional mechanisms of resistance to EGFR inhibitors exist. Therefore, additional biomarkers are needed to further optimise the selection of KRAS wild-type patients for personalized targeted therapy.

Methods: 45 patients (mean age: 61.4 years) with histologically proven metastatic colorectal adenocarcinoma were treated with either cetuximab or panitumumab. KRAS mutations were detected in 23 (51%) patients. In the 22 KRAS wild-type patients, the expression of signaling phosphoproteins belonging to Ras/Raf/MAPK pathway (pMEK1, pERK1/2, pP90RSK) and PI3K/AKT pathway (pAKT, pGSK3β, pP70S6K) as well as pP38MAPK and pEGFR were retrospectively analyzed using phosphoprotein array. KRAS wild-type patients were blindly classified as responders (complete response or partial response) or non responders (stable disease or progressive disease) using principal component analysis (PCA) based on phosphoprotein expression, followed by a linear discrimination analysis (LDA). Quality of classification was assessed by the leave-one-out method.

Results: As compared with KRAS status, PCA of phosphoprotein data had a higher sensitivity (97 vs 68%) and NPV (89 vs 50%), but lower specificity (73 vs

100%) and positive predictive value (PPV) (92 vs 100%). Mean LDA scores were significantly higher in responders patients (0.36±0.32) than in non responders (0.77±0.28) (P=0.003) and allow to blindly predict response in 81% KRAS WT patients.

Conclusion: Multiparameter analysis tools such as PCA are key approaches to evaluate multiple biomarkers. This is of particular concern with targeted therapies since their mechanism of action involves complex biological systems such as cell signaling. These preliminary results may emphasize the interest of evaluation of EGFR downstream functionality as predictive marker of response to anti-EGFR therapy.

Disclosure: All authors have declared no conflicts of interest.

590P INTER-OBSERVER REPRODUCIBILITY OF EVALUATION OF EGFR STATUS IN COLORECTAL CARCINOMA

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Background: According to European Medicines Agency, evaluation of EGFR status by immunohistochemistry is mandatory before treating metastatic colorectal cancer (mCRC) patients with Cetuximab. However EGFR status may depend on the detection methods and may be different in primary and metastatic samples of the same tumor. Furthermore patients with EGFR negative CRC may respond to Cetuximab. Thus many oncologists do not consider EGRF as relevant before Cetuximab therapy in KRAS non mutated mCRC patients. The present study aimed to determine the reproducibility of EGFR status evaluation.

Methods: EGFR status was assessed on the first 74 consecutive samples received for the central review of patients enrolled in the PETACC08 study. This clinical trial includes patients with stage III colon adenocarcinomas from 8 European countries (EU-20547, EUDRACT-2005-003463-23). EGFR expression was assessed centrally using the FDA approved Dako EGFR pharmaDx kit. The 74 slides were analyzed independently by three pathologists (CJ, FPL, SL), expert in digestive pathology and with a long experience in EGRF evaluation, without knowledge of other interpretations. Tumors were considered as positive when at least one tumor cell was stained. The Kappa coefficient (3 raters) was used to explore inter pathologist agreement.

Results: The 74 slides were all considered as good for evaluation by the 3 pathologists. The 3 interpretations were concordant in 58 cases (78%), with 93% positive and 7% negative tumors. The number of positive tumors according to each of the 3 pathologists were 58 (78%), 60 (81%), and 70 (95%), respectively. The number of non-concordant cases compared to the two other pathologists were 6 (8%), 4 (5%) and 6 (8%) for each pathologist, respectively. Inter-observer reproducibility kappa coefficient was 0.44 for negative/positive evaluation.

Conclusion: This work shows that inter-observer reproducibility among expert pathologists for EGFR status reading in CRC is low. Discrepancies are seen in more than 20% of the patients. Our results provide additional arguments not to use this test before treating patients with Cetuximab.

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All other authors have declared no conflicts of interest.

591P EUROPEAN REGLEMENTATION FOR CETUXIMAB STILL REQUIRED THE EGFR POSITIVE STATUS : RESULTS OF A FRENCH TRANSLATIONAL STUDY OMIT OF 330 PATIENTS TO DEFINE IF THIS CRITERIA IS RELEVANT.

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Methods: The OMIT (Drugs ant Emerging Therapeutics Observatory) is a french structure created in 2003 by the Regional Health Agency in Western (Bretagne and Pays de la Loire). This network collects data from 50 public hospitals and private institutions and the medical staff has a global reflection on the drugs management in cancer patients and publishes guidelines to optimize care. Moreover, the OMIT represents a task force for the French Health Autorities. Patients treated with cetuximab and irinotecan after irinotecan based regimen failure were included for metastatic colorectal cancer in the prospective database called Erbitux Ouest from the OMIT in 2005-2006 (n=537). For all cases, EGFR expression has been assessed with the three commercially available kits : the FDA approved Dako EGFR pharmaDx™ kit, the Zymed® EGFR kit and the Ventana® CONFIRM™ EGFR 3C6 antibody. Cases were defined as diffuse vs mosaic. Intensity was 1+, 2+ or 3+. Negative cases were considered if negative status was observed with Dako EGFR. Full negative patients (FNP) were defined as negativity for all three tests. EGFR CISH was performed systematically for full negative patients.

Results: 335 specimens from 330 patients among 537 included were analysed. In all cases, the three technics by IHC were successfully done. FNP were observed in 26.1% (86 patients among 330), full positive patients (FPP) in 59.1% (195 patients). Conflicting IHC results were found in 14.9%. In 43 cases, patients were Dako negative but positive for another antibody. In 6 cases, patients were DAKO positive but negative for another antibody All the patients with negative Dako were found CISH negative. The first clinical results show that, for FNP, objective response (21.3%) and stabilisation (RO+SD) were found in 54.1%. In case of FPP, RO (24.7%) +SD was 53.2%. Updated results and median overall survival will be presented at the meeting.

Conclusions: Results of EGRF status by IHC can depend on the choice of the EGFR antibody. More than 50% of full negative patients have a real clinical benefit. This Study OMIT tend to prove the lack of interest of EGFR status in the management of cetuximab treatment.

Disclosure: All authors have declared no conflicts of interest.

592P "DETERMINA KRAS" PROJECT: WHAT'S NEW AFTER TWENTY MONTHS?

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Background: A wealth of data indicates that patients with wild-type KRAS metastatic colorectal cancer (mCRC) derive meaningful clinical benefit from epidermal growth factor receptor (EGFR) inhibitors. The identification of KRAS mutation status as a predictive biomarker for the activity of anti-EGFR marked a turning point in the use of them. It changed the landscape of mCRC treatment by providing an improved patient-tailored approach. ASCO recognized it as a major advance in 2008 and it also gave a clinical opinion so every candidate for anti-EGFR therapy should be tested for KRAS mutations. NCCN guidelines recommends to do it at the first diagnose of metastatic disease. As reported in 2009, KRAS status testing was not widely available in Spain by 2008. The project Determina KRAS was developed in order to provide access to this test throughout the country to any patient. Results of almost two years of experience are shown.

Material and methods: Five well know Spanish centers were trained and provided with equipment so they could analyze KRAS status in a five working day period. First center was initiated in July 2008, being the last one in October 2008. A validated KRAS mutation kit (DxS Ltd, Manchester, UK) which identifies 7 different somatic mutations located in codons 12 and 13 using allele-specific real-time polymerase chain reaction was used.

Results: 10.555 samples from mCRC patients have been analysed since July 2008 (42% first line). 90% of samples were paraffin-embedded. There were no technical problems in 98% of cases. 53.7% samples showed wild- type KRAS status and G12D mutation was the most frequent mutation observed.

Conclusions: The introduction of KRAS testing to select patients who most likely will benefit from EGFR-targeted based therapy is widely regarded as a key advance in the field of personalized cancer medicine. A slight difference was observed in the percentage of patients harbouring KRAS mutation. No significant differences were observed in the type of mutations, compared with data in the literature. KRAS status testing is essential for treatment decision-making in mCRC and access to it must be guaranteed for any patient. It should be part of routine standard practice at the time of diagnosis or early in the course of management.

Disclosure: All authors have declared no conflicts of interest.

593P EVALUATION OF KRAS MUTATION STATUS IN PRIMARY COLORECTAL TUMOURS AND CORRESPONDING LIVER METASTASES

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Background: The efficacy of anti-EGFR therapy in metastatic colorectal cancer is limited to patients with KRAS wild-type tumours. KRAS mutation analysis is therefore assessed prior to the initiation of this treatment, and is usually performed on primary tumour tissue. However, only limited data is available on the concordance of this test between primary tumour and corresponding metastases. We assessed the concordance in KRAS mutation status in an adequately powered study of 330 primary colorectal carcinomas and their corresponding liver metastases.

Patients and methods: Patients with histological confirmed colorectal cancer who underwent surgical resection of the primary tumour and biopsy or surgical resection of the corresponding liver metastases in three Dutch hospitals were included. Each specimen was subjected to macroscopic dissection, DNA extraction and KRAS (mutation analysis codons 12 and 13).

Results: So far we have analyzed 255 matched primary tumours and liver metastases. 91 matched samples had a KRAS mutation (35.7%). In 9 cases (3.5%) we found a discordance between primary tumour and metastasis; in 5 cases the primary tumour had a KRAS mutation while the metastasis had a wildtype status and in 4 cases the primary tumour and the metastasis had a different KRAS mutation.

Conclusion: We found a high concordance of KRAS mutation status of 96.5% in primary colorectal carcinomas and their corresponding liver metastases. Therefore both primary tumours and metastases can be used for KRAS mutation analysis. Updated results on 330 patients will be presented at the meeting.

Disclosure: All authors have declared no conflicts of interest.

594P EVALUATION OF KRAS, BRAF AND PI3KCA IN SYNCHRONOUS AND METACHRONOUS METASTATIC COLORECTAL CANCER (MCRC)

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Background: The treatment strategy for MCRC must be based on the evaluation of the EGFR pathway mutational status. Aim of study was to evaluate the incidence of KRAS, BRAF and PI3KCA mutations in synchronous and metachronous MCRC and correlations with metastatic sites.

Methods: Consecutive patients (pts) with MCRC treated at the Oncology Unit of S.Orsola-Malpighi Hospital - Bologna, Italy, between January 2009 and April 2010 were submitted to KRAS, BRAF and PI3KCA evaluations. Mutational status analyses were performed in primary tumor or metastasis (mts) and centralized in 1 molecular biology laboratory. Genomic DNA was extracted from highly enriched paraffin-embedded tumor specimens. The status of KRAS (exon 2), BRAF (exon 15), and PI3KCA (exons 9/20) was ascertained by PCR amplification followed by direct sequencing.

Results: A total of 88 pts were evaluated (69 for PI3KCA). Pts characteristics: 54 (61.4%) M and 34 (38.6%) F; 60 (68.2%) colon and 28 (31.8%) rectum; 49 (55.7%) mts synchronous and 39 (44.3%) metachronous; 36 (40.9%) only liver mts and 62 (59.1%) multiple sites mts. Determinations were performed in 68 (77.3%) primary tumors and 20 (22.7%) tumor mts. Mutational status: 47 (53.4%) KRAS-wt and 41 (46.6%) KRAS-m, 80 (90.9%) BRAF-wt and 8 (9.1%) BRAF-m, 84 (95.5%) PI3KCA-wt and 4 (5.8%) PI3KCA-m. Colon tumors had 34 (54.4%) KRAS-wt and 26 (43.3%) KRAS-m; rectal tumors had 13 (46.4%) KRAS-wt and 15 (53.6%) KRAS-m. No significant difference in KRAS-m incidence was observed in pts with liver mts alone, 14 (38.9%), as compared with multiple visceral mts 27 (52%) (p 0.228). We observed KRAS-m in 25 (51%) pts with synchronous metastasis vs. 16 (41%) in metachronous (p 0.350). KRAS-m status in pts with synchronous/early metachronous mts (≤12 months from diagnosis) was 29 (46.8%) compared with 12 (46%) in late metachronous mts (p 0.958). Ten out of 12 (83.3%) pts with BRAF/PI3KCA mutations had synchronous mts at diagnosis.

Conclusions: Our results agree that KRAS is not a prognostic factor. No differences in KRAS mutational status were found between patients with synchronous and metachronous mts, and between liver and visceral multiple mts. A high percentage of BRAF/PI3KCA mutations was observed in synchronous mts.

Disclosure: All authors have declared no conflicts of interest.

595P KRAS MUTATIONAL STATUS IN JAPANESE PATIENTS WITH COLORECTAL CANCER: RESULTS FROM A MULTICENTER, CROSS-SECTIONAL, LARGE OBSERVATIONAL STUDY CONDUCTED BY THE JAPAN STUDY GROUP OF KRAS MUTATION IN COLORECTAL CANCER

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Background: The KRAS mutation mainly located in the codon 12 and 13 in colorectal tumors indicates unresponsiveness of patients with metastatic colorectal cancer (CRC) to anti-epidermal growth factor receptor (EGFR) antibodies. Various studies have reported that approximately 30–40% of CRC patients have KRAS mutations. However, the data on the frequency of KRAS mutation in Japanese CRC patients is limited to small sample size series. Objective: We aimed to elucidate KRAS mutational status in Japanese CRC patients in this multicenter, cross-sectional, observational study.

Methods: The key eligibility criteria included histologically confirmed colorectal adenocarcinoma with adequate tumor samples. Formalin-fixed paraffin-embedded tumor blocks or thinly sliced tumor sections from 389 centers were sent to commercial laboratories. Almost all KRAS point mutations in the codon 12 and 13 were investigated by direct sequencing.

Results: Between Oct. 2009 and Mar. 2010, 5,887 tumor samples were registered. As of the cut-off date, Apr. 2010, we have determined the KRAS mutational status of 5,668 samples (96%). The median age was 65 years old, and 61% were male. The primary tumor site was right colon, left colon, and rectum in 30, 38, and 32% patients, respectively; 92% were obtained from the primary site and 94% were surgically resected samples. The TNM stage at the time of sample collection was stage I, II, III, IV, and recurrence in 2.8, 14, 31, 49, and 2.7%, respectively; 96% were analyzed by direct sequencing. The frequency of KRAS mutation was 37.5% (2126/5668), and 80% (1691/2126) mutations were located in the codon 12.

Conclusion: This is the largest observational study of KRAS mutational status in CRC in Japan. The frequency of KRAS mutation in Japanese CRC patients is similar to those reported in previous studies from western countries. The latest data and the association between KRAS mutational status and baseline characteristics will be reported at the meeting.

Disclosure: All authors have declared no conflicts of interest.

596P EARLY TUMOR SHRINKAGE FOR THE PREDICTION OF EFFICACY OF CETUXIMAB IN METASTATIC COLORECTAL CANCER (MCRC): ANALYSIS FROM THE CRYSTAL STUDY

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Background: We have shown that early tumor shrinkage predicts long term outcome in chemorefractory mCRC treated with cetuximab monotherapy or in combination with chemotherapy (CT) in both unselected (BOND trial; Piessevaux et al Ann Oncol 2009) and selected (KRAS wild-type [wt]) patients (pts) (De Roock et al, Ann Oncol 2008). Thus early tumor shrinkage may be a hallmark of efficacy of EGFR inhibition and could be used as an on treatment marker of efficacy. In contrast in the AVF2107 and N9741 1st-line trials objective response did not predict the outcome benefit from standard CT or the addition of bevacizumab (Grothey et al J Clin Oncol 2008). The CRYSTAL study data show that adding cetuximab to FOLFIRI significantly improves overall survival (OS) (Hazards ratio (HR), 0.796, p=0.0093) in pts with KRAS wt tumors. In this present analysis we investigated tumor shrinkage at first evaluation as a predictor of long term outcome in KRAS wt pts from this study.

Methods: Based on the 8-weekly radiological assessments (RX) reported by the investigator and reviewed by an independent review committee (IRC), relative changes in tumor size from baseline were computed. Kaplan-Meier curves were computed for progression-free survival (PFS) and OS, stratified by treatment and KRAS status.

Results: A sensitivity analysis identified the best cut-off to use as a predictive variable for outcome to be a >20% RX decrease (tumor shrinkage) at week 8. Early tumor shrinkage was associated with a significantly better OS and PFS in KRAS wt pts receiving cetuximab plus FOLFIRI, but not for OS in FOLFIRI treated pts (test for treatment interaction p=0.032 and P<0.001 respectively) (Table).

Table. Early tumor shrinkage by treatment in KRAS wt pts*

	Early tumor shrinkage (<20% vs >20%)			
	FOLFIRI		cetuximab + FOLFIRI	
	<20% n=151	>20% n=125	<20% n=91	>20% n=159
PFS				
Median months [95% CI]	7.7 [6.9–8.3]	9.7 [8.6–10.7]	7.3 [5.5–9.0]	11.8 [9.6–14.0]
HR [95% CI] p-value	0.689 [0.495–0.957] 0.026		0.368 [0.256–0.529] <0.0001	
OS				
Median months [95% CI]	20.2 [15.3–25.1]	21.2 [16.7–25.7]	19.6 [17.3–22.0]	28.3 [24.6–31.9]
HR [95% CI] p-value	0.814 [0.626–1.059] 0.125		0.643 [0.480–0.862] 0.003	

*Measurement by IRC, not all KRAS wt pts in the CRYSTAL study (n=666) were evaluable at week 8

Conclusions: In the CRYSTAL study the presence of early tumor shrinkage in the KRAS wt population is predictive of optimal benefit for pts with mCRC treated 1st-line with cetuximab plus FOLFIRI. Ongoing analyses including associations with early skin rash will be presented.

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S. Heeger: declares being an employee of Merck KGaA
E. van Cutsem: declares having provided an advisory role and received research funding from Merck Serono
S. Tejpar: declares having received research funding from Merck Serono
All other authors have declared no conflicts of interest.

597P CETUXIMAB AND 1ST-LINE CHEMOTHERAPY IN ELDERLY AND YOUNGER PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC): A POOLED ANALYSIS OF THE CRYSTAL AND OPUS STUDIES

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Background: It has recently been demonstrated in a pooled analysis of data from the CRYSTAL and OPUS trials, that cetuximab significantly improves the overall survival (OS), progression free survival (PFS) and response rates when added to 1st-line treatment in patients (pts) with KRAS wild-type mCRC (Van Cutsem et al, Eur J Cancer Suppl 2009). As the median age of disease onset in mCRC is >70 years, we analyzed these studies to explore the effect of age on efficacy and safety of cetuximab and chemotherapy.

Methods: Individual data from KRAS wild-type pts treated in the CRYSTAL (FOLFIRI +/- cetuximab) and OPUS (FOLFOX +/- cetuximab) trials were analyzed for OS, PFS and safety in elderly (≥70 years) and younger (<70 years) pts.

Results: In younger pts with or without cetuximab, the median PFS was 10.0 vs. 7.7 months and median OS was 23.6 vs 20.2 months. Similar differences were observed in elderly pts with or without cetuximab: PFS was 8.9 vs 7.2 months and OS was 23.3 vs. 15.1 months, (Table). There were no differences in the 60-day mortality rates between patients in both age groups treated with or without cetuximab (Table). Grade 3/4 toxicity was increased in both treatment arms for elderly patients, but there was no obvious interaction between age (< 70 vs. ≥ 70 years) and the differences for treatment toxicity between the arms.

Conclusions: With a cut-off of 70 years, no major interference between age and efficacy of cetuximab in combination with standard chemotherapy or on the differences for toxicity was shown. Further analysis including additional safety and efficacy data is ongoing.

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Table Efficacy and safety in pts pooled from the CRYSTAL and OPUS studies

	Younger (<70 years) pts		Elderly (≥70 years) pts	
	Cet + CT n=320	CT n=380	Cet + CT n=78	CT n=67
Efficacy Median PFS (months) [95% CI]	10 [9.0–11.5]	7.7 [7.4–8.9]	8.9 [7.2–16.1]	7.2 [6.0–9.3]
Median OS (months) [95% CI]	23.6 [20.7–26.8]	20.2 [18.6-22.0]	23.3 [16.8–25.7]	15.1 [12.6–18.8]
Safety, n (%)	n=321	n=380	n=78	n=67
Grade 3/4 toxicity				
Neutropenia	100 (31.2)	90 (23.7)	26 (33.3)	24 (35.8)
Diarrhea	41 (12.8)	30 (7.9)	18 (23.1)	10 (14.9)
Fatigue	13 (4.0)	18 (4.7)	2 (2.6)	5 (7.5)
All skin toxicity	81 (25.2)	3 (0.8)	18 (23.1)	1 (1.5)
60-day mortality	7 (2.2)	8 (2.1)	1 (1.3)	2 (3.0)

Cet =cetuximab; CT= chemotherapy (FOLFIRI or FOLFOX)

598P THE ROLE OF HER-3 EXPRESSION IN THE PREDICTION OF CLINICAL OUTCOME FOR ADVANCED COLORECTAL CANCER PATIENTS RECEIVING IRINOTECAN-CETUXIMAB

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Pre-clinical data suggested that in presence of HER-3 altered activation colorectal cancer cells may escape anti-EGFR mediated cell death. HER-3 over-expression may then represent a key factor for resistance to anti-EGFR antibodies in colorectal cancer. Aim of our analysis was to investigate a possible correlation between HER-3 expression and clinical outcome in K-RAS wild type advanced colorectal cancer receiving cetuximab and irinotecan. We retrospectively analyzed immunoreactivity for HER-3 in K-RAS wild type advanced colorectal cancer patients receiving irinotecan-cetuximab Eighty-four advanced K-RAS wild type colorectal cancer patients were available for HER-3 analysis. Forty patients (48%) showed HER-3 negative colorectal tumor, whereas the remaining 44 cases (52%) were deemed HER-3 positive. In HER-3 negative and HER-3 positive tumors we observed a partial response in 17 (42%) and 8 (18%) patients respectively ($p = 0.04$). Progressive disease was obtained in 11 (35%) and 26 (53%) patients with respectively HER-3 negative and positive tumor ($p = 0.007$). No differences were observed for stable disease. Median PFS was 6.3 months in patients showing HER-3 negative tumors and 2.8 months for those who had HER-3 over-expressing tumors ($p < 0.0001$). Median overall survival was 13.6 months in patients showing HER-3 negative tumors and 10.5 months for those who had HER-3 expressing tumors ($p = 0.01$). HER-3 proved to be a predictive factor for clinical outcome in K-RAS wild type colorectal cancer patients treated with cetuximab Combined HER-3 and K-RAS analysis may represent an effective strategy for a better selection of responding colorectal tumors.

Disclosure: All authors have declared no conflicts of interest.

599P INCIDENCE AND PROGNOSTIC VALUE OF BRAF MUTATION IN METASTATIC COLORECTAL CANCER (CRC) WITH MISMATCH REPAIR DEFICIENCY (DMMR)

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Background: In stage II-III CRC the overall incidence of BRAF mutation and dMMR is 8% and 10-20%. The incidence of BRAF mutation in sporadic dMMR is high (24%, Roth et al, JCO 2010), and BRAF mutation in contrast to dMMR has a negative

prognostic value, although this may be restricted to BRAF mutation in association with MMR stable patients (pts). In metastatic CRC no data are available on the role of BRAF in relation to dMMR, which have an incidence of approx. 8% and 4%, resp. We investigate the incidence and outcome of BRAF and KRAS mutation in relation with dMMR in metastatic CRC pts treated in the DCCG CAIRO study (Koopman et al., Lancet 2007).

Methods: Expression of MMR proteins was examined by immunohistochemistry in the primary tumours of 515 pts. In addition microsatellite instability analysis was performed and the methylation status of the MLH1-promoter was assessed. The BRAF V600E mutation and the KRAS codon 12 and 13 mutation status were assessed by sequencing.

Results: In 18 dMMR pts we found a BRAF mutation in 12/17 pts (71%) and KRAS mutation in 2/17 pts (12%), in 2 pts one of the mutation analyses was technically not possible. Baseline pts characteristics in the mutated versus wildtype groups were comparable. 11/12 pts with BRAF mutation and 0/5 pts with BRAF wildtype had hypermethylation of the MLH1-promoter. 2/2 pts with KRAS mutation and 11/15 pts with KRAS wildtype had hypermethylation of the MLH1-promoter. Pts with a BRAF mutation vs. BRAF wildtype had a median overall survival of 6.8 vs. 19.8 months, respectively.

Conclusions: For the first time we investigated the role of BRAF in metastatic dMMR patients, and observed a higher incidence of a BRAF mutation in dMMR tumours compared to stage II-III disease. BRAF mutation in metastatic dMMR pts was only observed in sporadic dMMR cases, and appears to be a prognostic factor. This result should be confirmed in a larger data set.

Disclosure: All authors have declared no conflicts of interest.

600P MULTICENTER PHASE II STUDY OF SECOND-LINE?FOLFIRI+CETUXIMAB WITH KRAS WILD TYPE GENE IN METASTATIC CRC?FLIER)

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Aims and methods: The aim of this study is to evaluate the efficacy of second-line FOLFIRI plus cetuximab in KRAS wild type metastatic colorectal cancer. Primary endpoint is response rate and other secondary endpoints are PFS, OS and safety.

DNA was extracted from formalin fixed, paraffin embedded tissue. KRAS test(codon12,13) by direct sequence and UGT1A1 analysis were performed in Yamaguchi University. Patients with KRAS wild type were enrolled in this study. The dose of irinotecan was 150mg/ m2 (approved dose in Japan). The starting dose of irinotecan was decreased to 100mg/m2 with UGT1A1 *28,*6 homozygous or both heterozygous.

Results: After front line of FU plus oxaliplatin based chemotherapy, 112 patients were preregistred from December 2008 to November2009. Sixty seven patients with EGFR positive and KRAS codon 12, 13 wild were eligible. Patients with KRAS mutant (45/112, 40.2%) were excluded. Sixty patients were registered to this study. The incidence of UGT1A1*28, *6 homozygous was 2.8%, 4.7% respectively. Grade 3/4 adverse events were leucopenia 15.2%, neutropenia 25.4%, emesis 3.3%, skin toxicity(fissure, paronychia) 6.7%, and diarrhea 0%. The response rate is 30% and disease control rate is 84.0%.

Conclusion: FLIER is the first multicenter phase II trial with prospective KRAS analysis as a predictive biomarker for cetuximab in second-line mCRC in Japan. Second-line FOLFIRI plus cetuximab in KRAS wild type was well-tolerated and effective. Personalized therapy by KRAS is possible in Japanese clinical practice.

Disclosure: All authors have declared no conflicts of interest.

601P EFFICACY AND SAFETY OF CETUXIMAB PLUS IRINOTECAN IN IRINOTECAN-REFRACTORY ELDERLY PATIENTS (>65 YEARS) WITH METASTATIC COLORECTAL CANCER (MCRC)

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Background: Clinical trials may have a selection bias caused by an underrepresentation of pts older than 65 years (y) and of an ECOG performance status >1-2; 1. Non-interventional studies (NIS) are a helpful tool to evaluate approved therapies in daily practice in the general patient population. The aim of this subgroup analysis of a German NIS was to evaluate the efficacy and safety profile of cetuximab plus irinotecan in irinotecan pretreated mCRC patients aged < 65 and > 65 years.

Methods: Between 04/2005 and 11/2007 the data of 497 irinotecan-pretreated pts with mCRC (out of 657 pts documented) were entered in the database of this NIS. We analyzed both patient groups applying descriptive statistics and Ï‡2- or Fishers exact test.

Results: Median age was 66 y [30-88] with 247 and 250 pts of age < 65 and age > 65, respectively. 17.4% and 21.6% of pts in both groups showed an ECOG status of 2-3. Pts had 1-4 lines of previous chemotherapy: 26% and 17% 1 line, 43% and 43% 2 lines, 19% and 25% 3 lines, and 13% and 15% 4 lines (p=0.55). Severe cetuximab-related toxicity occurred in 2% (6 and 4 pts, respectively). The median duration of any grade of skin reaction (35 d) was in pts age < 65 significant longer (42 d), than in patients age > 65 (31 d); (p=0.04). However, there was a trend towards higher grade (â‰¥2) skin toxicity in pts age > 65. Skin toxicity led to discontinuation of therapy in 2.6% (6 pts in both groups), but in 22% and 31% to a dose modification and in 6% and 11% to a treatment pause. The objective response rates were similar for both groups: 38.1% for age < 65 vs. 36.4% for age > 65 (p=0.57). The rates for secondary resectability of metastases after cetuximab-based therapy were 4.4% for both groups. Time to tumor progression was similar for both age groups: 4 months [range: 1.0-19.0] and 5 months [1.0-17.0] (p=0.79).

Conclusion: Cetuximab has a similar efficacy and safety profile for pts age > 65 and < 65 y. Therefore these results add valuable information to the clinical trials..

Disclosure: All authors have declared no conflicts of interest.

602P SAFETY, PHARMACOKINETICS (PK), AND EFFICACY OF IMPRIME PGG PLUS CETUXIMAB (CETUX) WITH AND WITHOUT IRINOTECAN (IRINO) IN ADVANCED METASTATIC COLORECTAL CANCER (MCRC) PATIENTS

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Background: Imprime PGG (Imprime PGG® Injection) is a neutrophil-activating ß-glucan polymer being developed for treatment of cancer in combination with complement-activating monoclonal antibodies.

Methods: A sequential 2-arm study in mCRC patients (pts) evaluated the safety, PK and efficacy of escalating Imprime PGG doses administered in combination with cetux plus irino (Arm 1; N=10) or cetux alone (Arm 2; N=22, 21 evaluable). In 6-wk cycles, pts received weekly cetux (400 mg/m^2 loading, then 250 mg/m^2) and Imprime PGG (2 mg/kg, 4 mg/kg or 6 mg/kg, with safety review between doses) with or without irino (125 mg/m^2; wks 1-4 of each cycle). If available, primary tumor was assessed for KRAS status. Safety (primary endpoint) was assessed by adverse events (AEs); PK assessed using noncompartmental analysis of serum ß-glucan levels measured by a ß-glucan specific enzyme-linked immunosorbent assay; and efficacy assessed by response evaluation criteria in solid tumors.

Results: Pts were demographically comparable between study arms. Grade 3/4 AEs in > 10% of Arm 1 pts included diarrhea and neutropenia (50%), dehydration and hypokalemia (30%), and colitis, gastrointestinal obstruction, hyponatremia, ileus, and increased amylase (20%); those in > 10% of Arm 2 pts included hypokalemia and increased amylase (18%), and hyponatremia, increased aspartate aminotransferase, and increased gamma-glutamyltransferase (14%). Systemic exposure of ß-glucan was similar between study arms, suggesting irino did not affect the PK of Imprime PGG, and no significant accumulation of serum ß-glucan occurred after multiple weekly Imprime PGG dosings. In Arm 1, for all pts (N=10) and only KRAS wild type (WT) pts (N=7), the overall objective response rates (ORR) were 30 and 43% and the median times to progression (TTP) were 22 and 21 wks. In Arm 2, for all evaluable pts (N=21) and only KRAS WT pts (N=11), the ORRs were 24 and 45% and the TTPs were 12 and 24 wks.

Conclusions: Imprime PGG combined with cetux with or without irino was safe and yielded similar systemic ß-glucan exposure. Efficacy overall and in KRAS WT pts appears to be promising and warrants further investigation.

Disclosure: M.B. Tamayo and G.H. Cornelio: As co-PI on the study, was paid usual site investigator fees by the Sponsor (Biothera).J.P. Vasilakos, L.M. Marsh, R.M. Walsh, M.A. Gargano and M.L. Patchen: The author works for Biothera, the sponsor of the study. All other authors have declared no conflicts of interest.

603P EARLY MAGNESIUM MODIFICATIONS AS A SURROGATE MARKERS OF EFFICACY OF CETUXIMAB BASED ANTICANCER TREATMENT IN ADVANCED COLORECTAL CANCER PATIENTS

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Background: KRAS wild-type mutational status is necessary but not sufficient to get benefit from EGFR inhibition. Predictive markers are currently being evaluated including other EGFR downstream pathways and EGFR ligands. In the present study we investigated early hypomagnesemia as a predictor of efficacy and outcome in terms of TTP and OS in a selected cohort of patients affected by advanced colorectal adenocarcinoma KRAS wild-type cetuximab-treated.

Methods: 143 patients affected by stage IV and histologically confirmed colorectal adenocarcinoma KRAS wild-type receiving cetuximab+irinotecan as third-line anticancer treatment and resistant to oxaliplatin- and irinotecan-based chemotherapy were included. Magnesium plasma levels were measured before and the 1st, 7, 14, 21, 28 days after cetuximab + irinotecan infusion.

Results: The median magnesium basal value showed a statistically significant decrease after the start of cetuximab plus irinotecan anticancer treatment (at 28 days, P<0.0001). Patients with an early decrease of magnesium levels > 50% compared to the basal level had a higher tumor response rate (55.8% vs 16.7%, p<0.0001), a longer TTP (6.3 vs 3.6, p<0.0001) and a longer median OS (11.0 vs 8.1, p=0.002).

Conclusions: We have shown that early hypomagnesemia could be a predictor of efficacy and outcome in those patients harboring a wild type KRAS status treated with cetuximab + irinotecan. Magnesium circulating level is an easy and economically inexpensive biomarker to routinely and serially be detected in patients cetuximab-treated.

Disclosure: All authors have declared no conflicts of interest.

604P HYPOMAGNESEMIA RELATED TO ANTI-EGFR MONOCLONAL ANTIBODY THERAPIES: A POOLED ANALYSIS OF RANDOMISED TRIALS.

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Objective: it is well known that the anti-EGFR monoclonal antibodies cetuximab (C) and panitumumab (P) can be responsible for hypomagnesemia (hypoMg). The purpose of this meta-analysis was to determine the risk of all grades and severe grade (3-4) hypoMg in patients treated with C or P in randomised clinical trials.

Method: studies eligible for this metanalysis included those in which patients were randomly assigned to receive standard treatment (chemotherapy and/or radiotherapy) combined with C or P, versus standard treatment alone. Randomised phase II and III trials were included. The primary end-point of the metanalysis was risk of all grades and severe hypoMg. The relative risk was calculated for all studies together and each agent separately. Secondary end-points were the incidence of hypoMg and its risk according to the site of cancer.

Results: fourteen reports of randomised controlled trials were included for appraisal and data extraction. Two reports were phase II, and 12 were phase III randomised trials. The incidence of hypoMg was 0,17 in the study group (95% CI 0,16-0,18) and 0,03 in the control group (95% CI 0,027-0,039) (p< 0,0001). This incidence was 0,138 in P arms and 0,205 in C arms. Overall risk ratio for hypoMg was 5.1. Risk ratios were 11.5 and 3.4 respectively for the P and C arms. Severe diarrhoea afflicting patients in the two P trials could be responsible for the higher rates. Incidence of severe hypoMg was 0,034 and 0.0027 respectively, (p <0.0001), for treatment and control arms. In C arms this value was 0.04 and in P arms 0.028 (p for difference 0.046). Overall risk ratio for severe hypoMg was 8.3 being 7.48 for C and 10 for P . Head and neck cancer patients had a lower incidence of hypoMg (0.068).

Conclusion: the present metanalysis indicates that anti-EGFR therapies increase, significantly, the risk of all grade and severe grade hypoMg. The real clinical significance of this adverse event is unknown. No deaths or severe complications have been reported. Magnesium supplements and drugs to prevent diarrhoea are recommended precautions to be taken in patients at risk for such complications.

Disclosure: All authors have declared no conflicts of interest.

605P GENETIC POLYMORPHISMS OF THE FCγRIIA-FCγRIIIA ARE NOT PREDICTIVE OF CLINICAL OUTCOMES AFTER CETUXIMAB BASED CHEMOTHERAPY IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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Background: Cetuximab, anti-EGFR monoclonal antibody, is proved to be effective in patients with metastatic colorectal cancer (mCRC), and the KRAS status is a well-known molecular predictive biomarker. The antibody dependent cell-mediated cytotoxicty (ADCC), which is considered to be another action of mechanisms of cetuximab, is mediated by Fcγ receptor (FcγR) on the host immune cells. The FcγR gene polymorphisms have been studied recently as another possible predictive biomarker for cetuximab. This study investigated the clinical relevance of FcγR gene polymorphisms and KRAS status in irinotecan-refractory mCRC patients treated with cetuximab.

Patients and methods: A total of 123 irinotecan-refractory mCRC patients were screened for KRAS mutations (codons 12 and 13) using direct sequencing from paraffin-embedded samples. Gene polymorphisms for FcγRIIIa-158V/F and FcγRIIa-131H/R were analyzed using peripheral blood of 63 and 109 patients, respectively, by direct sequencing and multiplex allele-specific PCR. The results were correlated with response rate (RR), progression-free survival (PFS) and overall survival (OS).

Results: KRAS mutations were found in 33 patients (27.3%). The wild-type KRAS was associated with better RR (p<0.001), longer PFS (p<0.001), and longer OS (p<0.001). In terms of FcγR polymorphisms, FcγRIIa (H/H), (H/R), and (R/R) were found in 57, 47, and 5 patients, respectively. In addition, FcγRIIIa (V/V), (V/F), and (F/F) were found in 5, 21, and 37 patients, respectively. The clinical outcomes were not significantly different according to either FcγRIIa or FcγRIIIa polymorphisms. Likewise, the combined analysis with KRAS status did make no difference on the clinical effect of FcγR polymorphisms.

Conclusion: A KRAS status did influence the clinical outcome of mCRC patients treated with cetuximab, whereas FcγRIIa and FcγRIIIa polymorphisms did not. These results suggest that ADCC mediated by FcγRIIa and FcγRIIIa may not be the major mechanism of activity of cetuximab in mCRC patients.

Disclosure: All authors have declared no conflicts of interest.

606P CHEMOTHERAPY WITH OR WITHOUT BEVACIZUMAB IN ADVANCED COLORECTAL CANCER: A PHASE III TRIAL

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Abstract Objective: The objective of this Phase III trial was to compare chemotherapy combined with bevacizumab versus chemotherapy alone, in the treatment of patients with advanced colorectal cancer.

Methods: From September 2004 till September 2008, 222 treatment-naive patients were enrolled and divided into two Arms: 114 Arm A patients were treated with FOLFIRI and/or FOLFOX in combination with bevacizumab and 108 Arm B patients were treated with FOLFIRI and/or FOLFOX without bevacizumab. All patients were stage IV with histologically-confirmed adenocarcinoma.

Results: The median overall survival of Arm A patients was 22.0 months (95% CI 18.1-25.9) and 25.0 months (CI 18.1-31.9) for Arm B patients. There was no statistically significant difference between the two Arms (p value: 0.1391). No statistically significant difference between the two Arms regarding the response rate was observed: partial response, 36.84% and 35.19% for Arms A and B, respectively. Hematologic toxicity did not differ in the comparison of the two Arms. Non-hematologic toxicity in Arm A involved hypertension in 20.27% of the patients, proteinuria in 6.76%, 3 patients experienced hemorrhage and one patient, intestinal perforation. None of these side effects were observed in Arm B patients.

Conclusion: No statistically significant difference was observed in median overall survival in patients with advanced colorectal cancer treated with bevacizumab plus a combination therapy (Arm A) and those treated with the combination only, without bevacizumab (Arm B).

Disclosure: All authors have declared no conflicts of interest.

607P PHASE II TRIAL OF COMBINED CHEMOTHERAPY WITH IRINOTECAN, S-1, AND BEVACIZUMAB IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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Background: A study comparing the effectiveness and safety of irinotecan plus S-1 (IRIS) with that of a combination of 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) as second-line treatment in patients with advanced, recurrent colorectal cancer (FIRIS trial) is ongoing in Japan. We previously reported that IRIS is very effective as first-line treatment (33rd ESMO in 2008). Bevacizumab, a molecular targeted agent, is positioned as a standard regimen for the treatment of advanced colorectal cancer. We examined the effectiveness and safety of the IRIS regimen combined with bevacizumab.

Methods: Eligible patients had to have mCRC with a confirmed diagnosis of adenocarcinoma, an age of >20 years, a ECOG performance status (PS) of 0-1, and no history of prior chemotherapy. S-1 40-60 mg twice daily p.o. was given on days 1-14 and irinotecan 100 mg/m^2 and bevacizumab 5 mg/kg i.v. were given on days 1 and 15 of a 28-day cycle. The primary endpoint was safety. The secondary endpoints included overall response (OR), progression-free survival (PFS), and overall survival (OS).

Results: The target number of 53 patients was enrolled as of March 2009. The results are reported for 52 patients with evaluable lesions. The clinical characteristics of the patients were as follows. The median age was 63.5 years (range, 48 to 82). The male:female ratio was 3:2. The performance status on the Eastern Cooperative Oncology Group scale was 0. At interim analysis in January 2010, median number of treatment cycles was 8.5 cycles. On safety analysis, the incidence of grade 3 or 4 neutropenia was 25%. The incidences of other grade 3 or 4 adverse reactions were as follows: diarrhea, 15%; anorexia, 4%; stomatitis, 2%; hypertension, 19%; and gastrointestinal perforation, 0%. The overall response rate was 57.7%. Two patients had complete response. Twenty-eight patients had partial response, 18 had stable disease, none had progressive disease, and 4 were not evaluable. Median progression-free survival and overall survival are accumulated.

Conclusions: Our results suggest that IRIS plus bevacizumab is a well-tolerated, highly effective chemotherapeutic regimen that is easy to administer. The final data will be reported at this meeting.

Disclosure: Y. Komatsu: Taiho Pharmaceutical Co., Ltd. Chugai Pharmaceutical Co., Ltd YAKULT HONSHA CO., LTD. Merck Serono Takeda Pharmaceutical Co., Ltd Novartis

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All other authors have declared no conflicts of interest.

608P BEVACIZUMAB (BV) IN COMBINATION WITH FOLFOXIRI COMPARED TO BV PLUS FOLFIRI AS FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (MCRC): PRELIMINARY SAFETY RESULTS OF THE TRIBE STUDY BY THE GRUPPO ONCOLOGICO NORD-OVEST (GONO)

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Background: The triple drug combination FOLFOXIRI demonstrated increased activity and efficacy over FOLFIRI in a randomized trial (Falcone, JCO'07). The combination of FOLFOXIRI plus BV demonstrated promising results in phase II trials.

Methods: TRIBE is a multicenter, randomized, Italian trial. CRC patients (pts) with metastatic disease deemed unresectable were randomized to receive in first-line BV in combination with FOLFIRI (arm A) or with FOLFOXIRI (arm B) for a maximum of 6 months (induction treatment). In both arms a maintenance treatment with BV and fluoropyrimidines was scheduled. Primary end-point is progression free survival and the planned accrual is 450 pts.

Results: The trial is ongoing. We present the safety analysis of the first 150 randomized pts. Patients characteristics are (arm A/arm B): number 74/76, male gender 51%/59%, median age 59/58 years, ECOG PS=0 89%/87%, primary rectal 31%/28%, primary on site 26%/22%, multiple sites of metastasis 77%/66%. Administered cycles were: arm A 714 (median 12), arm B 724 (median 11). Main grade 3-4 observed toxicities are reported in the table. For arm A and arm B respectively Serious Adverse Events occurred in 15% and 20% of pts and, based on investigator judgment, possibly treatment-related deaths occurred in 3 pts (4%) [2 pulmonary embolism, 1 stroke] and 2 pts (3%) [1 GI bleeding, 1 sepsis].

Conclusions: These preliminary results demonstrate that both treatment arms are safe and feasible, side-effects occur with the expected incidence and there were not unexpected toxicities.

NCI-CTC 3.0 grade 3-4	Arm A (FOLFIRI+BV)		Arm B (FOLFOXIRI+BV)	
	N	%	N	%
Vomiting	0	0%	4	5%
Diarrhea	6	8%	15	20%
Stomatitis	4	5%	7	9%
Neutropenia	10	14%	36	47%
Febrile Neutropenia	3	4%	5	7%
Neurotoxicity (g2-3)	NA	NA	17	22%
Asthenia	6	8%	5	7%
Hypertension	1	1%	1	1%
Bleeding	0	0%	2	3%
Venous Thrombosis	6	8%	7	9%
Arterial Thrombosis	1	1%	2	3%
GI Perforation	0	0	1	1%

Disclosure: All authors have declared no conflicts of interest.

609P EFFICACY AND SAFETY OF SECOND-LINE BEVACIZUMAB (BV) PLUS FOLFIRI / FOLFOX IN PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC) WHO FAILED PRIOR-COMBINATION CHEMOTHERAPY WITHOUT BV: MULTICENTER RETROSPECTIVE 2ND-BV STUDY IN TSUKUBA CANCER CLINICAL TRIAL GROUP (TCTG)

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Background: Second-line BV + FOLFOX after chemotherapy with irinotecan and a fluoropyrimidine significantly prolongs overall survival (OS) and progression-free survival (PFS) in patients (pts) with mCRC (E3200 trial). However, the second-line BV+FOLFIRI after failure in FOLFOX has not been reported. We studied retrospectively the efficacy and safety of the second-line BV+FOLFOX / FOLFIRI in pts who failed in prior-combination chemotherapy without BV.

Methods: Patients who received second-line BV+FOLFIRI / FOLFOX between July 2007 and March 2008 were retrospectively included. Tumor response and disease progression were assessed by investigators.

Results: 139 pts were enrolled in 26 institutions. Median age: 62 years, male: 65%, ECOG PS 0 / 1: 72%/27%. Metastatic sites: liver (57%) / lung (48%), number of metastatic site: 1 site (47%) / 2 sites (40%) / >2 (13%). 104 pts were treated with BV+FOLFIRI after the first-line oxaliplatin-containing chemotherapy, and 35 pts were treated with BV+FOLFOX after the first-line irinotecan-containing chemotherapy. Median follow-up was 17.9 months. 89% of pts had disease progression. The mortality rate within 60-days after treatment completion was 6.5%. One treatment-related death (interstitial pneumonitits) was reported in BV+FOLFIRI group. BV-related grade > 3 adverse events were bleeding (5.0%), hypertension (4.3%), venous thromboembolism (2.2%) and proteinuria (0.7%). Response rate, median PFS, time to treatment failure and OS were 27%, 7.5 months (95%CI; 6.0 – 9.2), 7.2 months and 23.1 months in the BV+FOLFIRI group, and 31%, 7.4 months (95%CI; 5.9 – 9.0), 7.2 months and 18.5 months in the BV+FOLFOX group, respectively.

Conclusion: BV+FOLFIRI showed similar efficacy to BV+FOLFOX in second-line chemotherapy, and safety of additional BV with FOLFOX / FOLFIRI were suggested in clinical practice in Japan.

Disclosure: I. Hyodo: Advisory board member of Yakult, Taiho and Chugai Pharmaceutical Company. Corporate-sponsored research of Taiho Pharmaceutical Company.

All other authors have declared no conflicts of interest.

610P IMPACT OF KRAS AND BRAF GENE MUTATION STATUS ON OUTCOMES FROM THE PHASE III AGITG MAX TRIAL OF CAPECITABINE (C) ALONE OR IN COMBINATION WITH BEVACIZUMAB (B) +/- MITOMYCIN C (M) IN ADVANCED COLORECTAL CANCER (CRC)

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Background: Mutations affecting KRAS and BRAF genes are established predictive markers of outcome with anti EGFR antibodies in advanced CRC. The relevance of these markers for anti-VEGF therapy is controversial. This analysis was performed to assess the predictive and prognostic impact of KRAS and BRAF gene mutation status in patients receiving C +/- B +/- M in the randomised phase III AGITG MAX study.

Methods: DNA was extracted from archival formalin fixed paraffin embedded tumour tissue from 314 (66.7%) of the original 471 patients participating in the study. Mutation status was determined using high resolution melting point PCR and confirmed with direct sequencing (for equivocal KRAS and all BRAF). Mutation status was correlated with efficacy outcomes (RR, PFS and OS). Predictive analyses were undertaken using a test for interaction involving both C v CB and C v CB + CBM.

Results: Patient demographics and clinical outcomes were comparable between the tissue study population and the intent to treat population from the primary trial. Mutations in KRAS and BRAF genes were observed in 28.7% and 10.9% of patients respectively. KRAS gene mutation status (WT v MT) had no prognostic impact for PFS (HR 0.89, CI 0.69-1.14) or OS (HR 0.97, CI 0.73-1.28). In contrast BRAF mutation status (WT v MT) was not prognostic for PFS (HR 0.79, CI 0.54-1.16) but was prognostic for OS (HR 0.52, CI 0.35-0.78 p=0.002). Using the comparison of C v CB + CBM, KRAS gene mutation status was not predictive of the effectiveness of B for PFS or OS (test for interaction p=0.95 and 0.43, respectively). Similarly, BRAF gene mutation status was not predictive of the effectiveness of B for PFS or OS (test for interaction p=0.51 and 0.70, respectively). Similar results were observed with the comparison of C v CB.

Conclusion: KRAS gene mutation status was neither prognostic for OS nor predictive of bevacizumab outcome in patients with advanced CRC. BRAF gene mutation status was prognostic for OS but was not predictive of outcome with bevacizumab.

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611P CURRENT CHEMOTHERAPY AND MONOCLONAL ANTIBODY USE PATTERNS IN METASTATIC COLORECTAL CANCER IN WESTERN EUROPE

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Background: Treatment outcomes improved in metastatic colorectal cancer (mCRC) due to the introduction of the monoclonal antibodies (mAb) in combination with chemotherapy. This study described current treatment patterns of chemotherapy and mAbs in clinical practice in 4 EU countries.

Methods: This cohort study used physician-surveyed data from the LifeLink™ Oncology Analyzer Database for mCRC patients in 4 EU countries (France, Germany, Italy, and Spain). All patients aged ≥21 years at mCRC diagnosis were included. Treatment patterns in 2009 were examined descriptively by lines of therapy.

Results: The study sample includes 2,734 mCRC patients (61% male, median age category 61-70 years) with 862, 656, 567 and 649 from France, Germany, Italy, and Spain, respectively. In 1st-line, more patients received FOLFOX-containing regimens than FOLFIRI-containing regimens in Germany (42% vs 30%) and Spain (25% vs 16%), while in Italy and France the reverse was true (Italy: 34% FOLFIRI vs 29% FOLFOX: France: 26% vs 19%). In 2nd-line, more patients received FOLFIRI-containing regimens than FOLFOX-containing regimens in Germany (36% vs 18%), Italy (29% vs 14%), and Spain (34% vs 6%), while similar proportions of FOLFOX and FOLFIRI were used in France (18% vs 15%). In 1st line, bevacizumab was administered to 44% of the patients in Italy, 42% in France, 37% in Germany and 30% in Spain, while cetuximab use ranged from 14% in Spain to 7% in Italy. In 2nd-line, bevacizumab was administered to 37% of the patients in Germany, 38% in France, 33% in Italy and 30% in Spain while cetuximab was used in 30% of the patients in Spain, followed by 26% in Italy, 20% in Germany and 17% in France.

Conclusions: FOLFOX- and FOLFIRI–based regimens are common standard of care chemotherapies, and monoclonal antibodies are routinely combined with these chemotherapies.

Disclosure: Z. Zhao, B. Barber, S. Wang and S. Gao: I am a current employee of Amgen and hold Amgen stock; E. Pelletier, M. Bhosle and D. Klingman: I am currently conducting research sponsored by Amgen.

612P CLINICAL AND ECONOMIC BURDEN OF TOXICITIES ASSOCIATED WITH MONOCLONAL ANTIBODIES FOR METASTATIC COLORECTAL CANCER (MCRC)

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Background: As overall survival improves with newer therapies for mCRC, treatment-limiting toxicities and related costs will be important when evaluating treatment decisions. Little is known about toxicity-related cost of currently available monoclonal antibody treatments. This study was designed to identify cetuximab-, bevacizumab-, and panitumumab-related toxicities and estimate direct costs of treating these toxicities.

Methods: A comprehensive literature search was performed to identify English-language phase II / III studies of monoclonal antibodies for mCRC. The search utilized PubMed, conference abstracts, treatment guidelines, and product labels. Commonly reported grade 3 and 4 toxicities were identified, and outpatient and inpatient costs were estimated for all toxicities. Outpatient costs were estimated by applying 2010 Medicare reimbursement rates to resource use assumptions (assessed based on in-depth clinical interviews). Inpatient costs were estimated using ICD-9 codes and 2007 Medicare payments from the HCUP database; then were converted to 2010 values using the Consumer Price Index for medical care services.

Results: Clinically significant toxicities associated with bevacizumab include hypertension, arterial thrombosis, hemorrhage, gastrointestinal (GI) perforation, fistula, and wound healing complication; while treatment-related toxicities associated with cetuximab and panitumumab include skin rash, hypomagnesemia and infusion reactions, although the incidence of these toxicities differ between the two drugs. Cost of toxicities treated in outpatient setting ranged from $185 (hypertension and skin rash) to $585 (wound healing complications). Inpatient cost per event for GI perforation is the highest at $32,443, followed by fistula $29,062, arterial thrombosis $20,346, wound healing complication $13,240, hemorrhage $12,956, infusion reaction $10,877 and hypertension $8,453, while inpatient cost per event for skin rash and hypomagnesemia is among the lowest at $4,424 and $6,174, respectively.

Conclusion: Monoclonal antibodies have different toxicity profiles and the costs associated with managing these toxicities vary greatly.

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J. Munakata: IMS Health has received consulting fees from Amgen, the corporate sponsor of this research; B. Barber: Author is an employee of Amgen, the corporate sponsor of this research.

613P PERFUSION COMPUTED TOMOGRAPHY AS PROGNOSTIC AND PREDICTIVE FACTOR IN PATIENTS WITH COLORECTAL CANCER LIVER METASTASES TREATED WITH BEVACIZUMAB

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Background: Since anti-angiogenic treatment may induce necrosis with no change in tumor volume, new imaging methods are particularly suitable for the assessment of the response, for which the RECIST size criteria appear inappropriate. Perfusion Computed Tomography (CTp) scan has recently been proposed for evaluating therapeutic response, demonstrating changes in tumor parenchymal perfusion and emergence of necrosis even with no change in tumor volume. The aim of the study was to use the quantitative functional information and high spatial resolution of CTp to study neovascolarization of hepatic metastases.

Patients and methods: CTp was used to prospectively evaluate 48 hepatic lesions in 15 patients (male 10, female 5; age range 44-78 years, mean 58.2 years) with metastatic colorectal adenocarcinoma receiving bevacizumab since January 2008. CTp scan was

performed the day before (day -1) starting antiangiogenic therapy and at days 90 and 180. The tumor perfusion parameters evaluated were blood flow (BF), blood volume (BV) and capillary permeability surface area (PS).

Results: Tumor blood flow at baseline was inversely associated with patient progression-free survival. Compared with baseline, bevacizumab induced a significant decrease in the estimated parameters BF, BV and PS on days 90 and 180. Mean change in BF was 54%, in BV 35% and PS 59%. Patients with progressive disease had a lower percent decrease in all parameters than those with stable disease or partial response.

Conclusion: CTp allow evaluation of tumour angiogenesis in vivo. Patients with highly vascularized liver metastases as shown by high baseline tumor BF appear to have a worse prognosis than those who do not. Baseline and percent change in BF, BV and PS by CTp scan following bevacizumab administration correlated with clinical outcome.

Disclosure: All authors have declared no conflicts of interest.

614P A BLINDED PLACEBO (P) CONTROLLED PHASE 1/2 DOSE ESCALATION STUDY (DES) OF BRIVANIB (B), AN ORAL SELECTIVE DUAL INHIBITOR OF FGF AND VEGF SIGNALING, IN COMBINATION WITH CETUXIMAB (C) AND IRINOTECAN (I) IN PATIENTS (PTS) WITH KRAS WILD TYPE (KWT) ADVANCED OR METASTATIC COLORECTAL CANCER (AMCRC): SAFETY, TOLERABILITY AND PHARMACOKINETICS (PK) FINDINGS

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Background: B has therapeutic potential in a variety of tumors. B+C treatment is currently being tested in phase 3 in refractory amCRC. An innovative phase 1 design was used to determine if adverse events (AEs; eg, thrombosis-related events [TRE]) were higher with B combinations than the background rate.

Methods: A site-subject blinded, P-controlled phase 1/2 DES of B+C+I (BCI) in pts with KWT amCRC. A minimum of 4 pts per cohort were treated with BCI and 2 pts per cohort were treated with P+C+I (PCI). Standard full-dose I (q3w) and C (qw) were combined with escalating doses of B (200, 400, 600, 800 mg) PO qd.

Results: 28 pts received 200 (6), 400 (8), 600 (10), or 800 (4) mg of BCI or PCI for a median of 14 weeks (range 1–38). 1 dose-limiting toxicity (DLT), grade (gr) 3 diarrhea, occurred at 600 mg; 2 DLTs occurred at 800mg (gr 4 neutropenia >7days, gr 3 diarrhea). An unblinded safety review was conducted by the data safety monitoring committee. Blinded safety data are presented here. AEs (regardless of relationship) occurred in 25/28 pts and are consistent with monotherapy toxicities from B, C, and I. Notable is the incidence of gr 3 diarrhea (8/28; 28.6%) and gr 3/4 neutropenia (6/28; 21.4%), which is comparable to observed rates with I (q3w) and was similar between P and B treated pts. 3/28 pts experienced a TRE (all asymptomatic: portal vein, inferior vena cava (2)). No pts discontinued (DC) due to treatment-related AEs. 10 pts were not evaluable for response (5 DC before first evaluation, 5 in first 6 weeks), 10 pts had stable disease, 6 had a partial response, and 2 had progressive disease.

Conclusion: The safety profile of BCI in amCRC pts is manageable and seems consistent with monotherapy toxicities; there is no increased rate of TRE. Main toxicities (diarrhea, neutropenia) are I related and similar between P and B arms. A regimen with C, lower dose I (300mg/m2 q3w) and 800mg of B is currently being tested to mitigate the observed toxicities. Unblinded safety data and PK data will be presented at the meeting.

Disclosure: A. El-Khoueiry: Consultant/Advisory relationship with Bristol-Myers Squibb; received honoraria and research funding from Bristol-Myers Squibb. J.M. Chemidlin: Employee of Bristol-Myers Squibb; stock/ownership interest in Bristol-Myers Squibb. G. Kollia: Employee of Bristol-Myers Squibb; stock/ownership interest in Bristol-Myers Squibb. D.S.A. Nuyten: Employee of Bristol-Myers Squibb; stock/ownership interest in Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

615P A PHASE II STUDY OF CEDIRANIB IN COMBINATION WITH MFOLFOX6 IN JAPANESE PATIENTS (PTS) WITH METASTATIC COLORECTAL CANCER (CRC)

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Background: Cediranib (AZD2171) is an oral, highly potent inhibitor of all three VEGFRs. Phase I study results showed cediranib 20 or 30 mg + mFOLFOX6 was generally well tolerated in Japanese pts with CRC (Yamaguchi et al). This randomized, double-blind, Phase II study assessed the efficacy of cediranib + mFOLFOX6 vs mFOLFOX6 alone in Japanese pts with previously untreated advanced CRC.

Methods: Eligible pts (≥18 years, measurable disease, PS 0–1, adequate organ function) were randomized to once-daily cediranib (20 or 30 mg) or placebo (P) + mFOLFOX6 every 2 weeks (oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2, 5-FU 400 mg/m^2 bolus and then 2400 mg/m^2). Adverse events (AEs) were evaluated according to CTCAE v3.0. The primary objective was to assess progression-free survival (PFS). Secondary objectives included objective response rate (ORR), overall survival (OS) and safety/tolerability.

Results: Between Jan 2008 and Jan 2009, 172 pts (female [38%], PS 0/1 [78%/22%]) were randomized in this study (n=58, 56 and 58 in the cediranib 20, 30 mg and P arms, respectively). Baseline characteristics were generally balanced across the three arms. For the PFS comparison of 20 mg vs P the HR was 0.7 (0.44-1.11) and P=0.167, which met the criteria of P<0.2 defined in the protocol. The median PFS was improved by 2 months (10.2 vs 8.3 months). Whereas for the PFS comparison of 30 mg vs P the HR was 0.82 (0.54–1.31) and P=0.261, which did not meet the criteria. ORR was 53.4%, 69.6% and 50.0% in the 20, 30 mg and P arms, respectively. The median duration of response was 9.2, 6.7 and 7.1 months for 20, 30 mg and P, respectively. More patients stopped oxaliplatin >12 weeks before progression on 30 mg (33%) compared with 20 mg (14%) or P (8%). The incidence of grade 3/4 AEs was 66%, 75% and 36% in the 20, 30 mg and P arms, respectively. AEs leading to discontinuation were higher (27%) in the 30 mg arm vs 7% for 20 mg and 0% for P. Overall, the most common AEs throughout the study were diarrhoea and hypertension. No new safety issues were identified.

Conclusions: This study met its primary endpoint for improved PFS for the addition of cediranib 20 mg to mFOLFOX6 in Japanese patients with first line CRC with an acceptable tolerability profile.

Disclosure: All authors have declared no conflicts of interest.

616P PHASE II STUDY OF FIRST-LINE SUNITINIB (SU) IN COMBINATION WITH IRINOTECAN, LEUCOVORIN, AND 5-FLUOROURACIL (5-FU) (FOLFIRI) IN JAPANESE PATIENTS (PTS) WITH UNRESECTABLE/METASTATIC COLORECTAL CANCER (MCRC)

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Background: FOLFIRI is a standard first-line treatment for CRC. The oral, multitargeted tyrosine kinase inhibitor SU has shown preliminary single-agent efficacy in previously treated CRC.

Methods: Japanese pts with confirmed unresectable/metastatic CRC with no prior chemotherapy for metastatic disease were enrolled in this phase II, multicentre, open-label, single-arm study. Pts received FOLFIRI (irinotecan 180 mg/m^2 + l-leucovorin 200 mg/m^2, followed by bolus 5-FU 400 mg/m^2 then 2400 mg/m^2 as a 46-hr infusion) q2w with SU 37.5 mg/day on Schedule 4/2 (4 wks on, 2 wks off), until disease progression or study withdrawal. Primary endpoint: progression-free survival (PFS). Secondary endpoints: overall survival (OS), objective response rate (ORR) and safety.

Results: 71 pts (mean age 58 yrs [range 26–78]; 59% male) were enrolled and started a median of 3 (range 1–9) SU cycles. Mean SU dose intensity was 60.4%. To date, 37 pts (52.1%) had objective progression and 1 pt (1.4%) died without progression. Median

PFS was 6.3 mths (95% CI, 4.6–9.2) by independent central review and 7.1 mths (95% CI, 5.2–8.0) by investigator assessment. Median OS has not yet been reached. ORR was 33.8%/35.2% (24/25 partial responses), and the rate of best response ≥ stable disease was 78.9%/78.9% by independent review and investigator assessment, respectively. Common all-causality adverse events (AEs) were leukopenia (97.1%), neutropenia (95.7%), thrombocytopenia (84.5%), nausea (78.9%), diarrhoea (76.1%), decreased appetite (71.8%), fatigue (64.8%), alopecia (62.0%) and vomiting (53.5%). Grade (G) 3/4 AEs, respectively, included leukopenia (57.7%/9.8%), neutropenia (43.7%/49.3%), thrombocytopenia (22.5%/7.0%), lymphopenia (16.9%/1.4%) and febrile neutropenia (22.5%/0%). The study was terminated early due to findings from a concurrent phase III study of SU + FOLFIRI vs. FOLFIRI in non-Japanese pts with mCRC.

Conclusions: SU + FOLFIRI showed activity in patients with mCRC but was associated with a high incidence of AEs. Median PFS of SU + FOLFIRI was similar to historical PFS data with FOLFIRI alone in Japanese patients.

Disclosure: A. Tsuji: has had research funding and has been paid honoraria in the two years prior to trial accrual, by an entity that has a commercial interest in the subject matter; T. Denda: has had research funding from Pfizer Inc; T. Satoh: has had research funding from Pfizer Inc. in the two years prior to accrual; M. Yoshida, Y. Nishina, M. Nagase and K. Muro: has had research funding from Pfizer Inc. in the two years prior to this date; T. Kato: has received funding from Pfizer Inc. in the two years prior to this date; Y. Komatsu: has had research funding from Pfizer Inc., Merck Serono, GlaxoSmithKline, Yakult, Taiho Pharmaceutical LTD and Daiichi-Sankyo. All other authors have declared no conflicts of interest.

617P SORAFENIB (S) WITH FOLFIRI AS FIRST LINE THERAPY FOR METASTATIC COLORECTAL CANCER (MCRC): A PHASE I STUDY

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Abstract: Background: FOLFIRI is a standard treatment for mCRC. S has antitumor activity against mCRC. Drug-drug interactions occur between S and irinotecan (I). This study is to determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), recommended phase II dose (RP2D) of sorafenib and FOLFIRI combination, safety at the RP2D in an expanded cohort and pharmacokinetics (PK).

Methods: Cohorts of 3-6 patients (pts) with unresectable mCRC receive escalating doses of S and I (in a I dose reduced within FOLFIRI combination). Starting doses: I 80mg/m^2 iv d1, S 200mg po bid continuously, starting d2 (to allow baseline I PK sampling). Dose escalations are based on toxicity observed at the previous dose level (DL) up to S 400mg bid and I 100mg/m^2. DLT was defined as occurring within the 1st study cycle (cycle = 2 FOLFIRI treatments over 28 days). I PKs were collected at 7 timepoints on d1 and d9 of cy1.

Results: 3 cohorts were concluded. Of 10 ECOG PS 0-1 pts (7 men, 3 women; 2 rectal, 8 colon) with median age of 66, 3 discontinued study: 2 disease progression, 1 Gr3 toxicity hand-foot syndrome (HFS), neutropenia. Four pts were enrolled in DL1 (pt #3 was not evaluable for DLT and PK), 3 in DL2 (I 80mg/m2, S 600mg) and 3 in DL3 (I 90mg/m2, S 600mg). No pts in the first 3 DLs had cycle 1 DLT. The most common ≥Gr2 treatment induced adverse events (AEs) are: HFS, leucopenia 70%, anemia 40%, constipation, anorexia, fatigue, diarrhea, nausea, vomiting 30%. The most severe treatment induced AEs are: Gr4: 1 neutropenia; Gr3: 6 HFS, 2 neutropenia, 1 diarrhea, hypertension, hypophosphatemia, vomiting. Best objective responses in 9 evaluable pts (pt #10 not yet evaluable) include 5 PR (8+, 8+, 7, 6+, 3+ months), 3 SD (3+, 2+, 2 months), and one DP. Results of the PK analysis evaluating the effect of S on kinetic parameters of I and its metabolites, and its correlation with adverse events will be interpreted at the end of the escalation phase.

Conclusions: Combination therapy with S and modified FOLFIRI in these patients was well-tolerated, supporting the potential feasibility of this combination. Anti-tumor activity for the combination has been observed. Accrual continues with a 4th cohort planned. Supported by Bayer Healthcare Pharmaceuticals

Disclosure: J.A. Maroun: Member on Advisory board: Roche Corporate-sponsored research with Roche Honoraria: Roche
All other authors have declared no conflicts of interest.

618P A PHASE II STUDY OF TWO DOSE LEVELS OF VORINOSTAT (V) IN COMBINATION WITH FLUOROURACIL (5-FU) AND LEUCOVORIN (LV) IN FLUOROPYRIMIDINE-REFRACTORY COLORECTAL CANCER (CRC) PATIENTS (PTS)

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Background: V, a histone deacetylase inhibitor, synergizes 5-FU antitumor activity in preclinical models. We have previously investigated a QD x 3 schedule of V in combination with Q2W infusional 5-FU/LV. Prolonged stabilizations and a response were noted in 5-FU refractory CRC (pts) at V doses of 800mg and higher, warranting further investigation in phase II studies.

Methods: This is randomized 2-stage design phase II study of 800 mg (Arm 1) vs. 1400 mg (Arm 2) of V QD x 3 in combination with 5-FU/LV (LV 400mg/m^2, 5-FU 400mg/m^2 bolus, 5-FU 2400mg/m^2 46 hrs infusion) on days 2-3 of V, repeated Q2W. Randomization was stratified based on LDH and ECOG status. Eligible pts are those who progressed on standard chemotherapy and within 4 weeks of a fluoropyrimidine-based regimen. 30 pts are randomized on the 1st stage. Progress to stage 2 in either arm (additional 28 pts/arm) is to occur only if > 8/15 pts were progression free at 2 months (m). The primary end point is 2 m progression free survival (PFS) rate. Secondary endpoints include safety, response rate, and V pharmacokinetics (PK).

Results: 30 pts were enrolled. Median age was 58 and 63 years, females pts were 8 and 9, ECOG 0-1 pts were 11 and 12, pts with normal LDH were 7 and 9, in Arms 1 and 2, respectively. 9/15 pts were 2 m progression-free on Arm 1 vs. 8/15 on Arm 2. Only 1 partial response was encountered so far and is on Arm 1. Treatment related toxicities ≥ grade (G) 3 included 1 G3 fatigue and 1 G4 pulmonary embolism on Arm 1 and 3 G3 fatigue, 1 G3 anorexia, 1 G3 diarrhea, 1 G3 pneumonia, and 1 G3 dizziness on Arm 2. Serial EKGs (2, 4, and 6 hrs post 1st dose of V) on arm 2 showed 4/10 G2 QTc prolongations (all G1 baseline). No difference was noted in V PKs between arms (C_{max} = 3.01 +/- 2.49 on Arm 1 vs. 3.89 +/- 1.61 μM on Arm 2; $AUC_{0.5-8hrs}$ = 13.15 +/- 10.44 on Arm 1 vs. 15.59 +/- 9.84 h*μM on Arm 2). Substantial inter-patient PK variability was noted.

Conclusions: Encouraging 2-m PFS was noted with V + 5-FU/LV in chemo-refractory CRC. No advantage of higher oral doses of V could be documented in terms of PK or efficacy. Accrual will continue on the second stage of the study on Arm 1 only.

Disclosure: All authors have declared no conflicts of interest.

619P ANALYSIS OF PLASMA BIOMARKERS, DCE-MRI, AND KRAS MUTATIONS IN PATIENTS (PTS) WITH ADVANCED COLORECTAL CARCINOMA (CRC) TREATED WITH THE MULTIKINASE INHIBITOR REGORAFENIB

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Background: Regorafenib is a novel diphenylurea oral multikinase inhibitor of angiogenic (VEGFR1-3, TIE2), stromal (PDGFR-β, FGFR), and oncogenic kinases (KIT, RET, RAF). In in vivo models, regorafenib has shown a broad spectrum of antitumor activity. Regorafenib showed clinical activity in renal cell carcinoma and in a Phase I CRC study, for which biomarker results are given here. A Phase III study in pts with advanced CRC is ongoing.

Methods: Biomarker analyses presented here are from a Phase I study of regorafenib, given orally in repeating cycles (Cs) of 21 days (d) on/7 d off, in pts with refractory CRC. Plasma levels of VEGF and soluble VEGFR-2 (sVEGFR-2) were analyzed pre- and 8 h postdose on d 1 and 21 of C 1, predose on d 1 and 21 of C 2 and 3, predose on d 1 of all subsequent Cs, and at the final visit using the relevant quantitative ELISA. DCE-MRI was assessed at screening, on d 2 of C 1, d 21 of C 1 to 4, every 2nd C thereafter, and at final visit. KRAS mutations were analyzed using archival tumor samples and/or plasma samples obtained during the study. Tumor response was evaluated per RECIST. Biomarker and DCE-MRI were correlated to progression-free survival (PFS).

Results: 38 pts with actively progressing CRC were treated with regorafenib at doses of 60 mg (n=1), 120 mg (n=4), 160 mg (n=26), and 220 mg (n=7) once daily. The iAUC60s of Gd-DTPA as measured by DCE-MRI decreased over the course of the study (% change [arithmetic mean] to baseline d 2: -6.7%; d 21: -34.1%; d 49: -37.9%). VEGF plasma levels (change in arithmetic mean) increased by 62.4% (d 21) and 95.6%

(d 49), sVEGFR decreased by 35.8% (d 21) and 42.8% (d 49). KRAS mutations were found in 19/36 of evaluable pts (53%). Pharmacodynamic changes in DCE-MRI, VEGF and sVEGFR-2 were not correlated to PFS. Pts with mutated or wildtype KRAS were equally distributed among those who clinically benefitted (PFS ≥100 d).

Conclusions: Observed changes in angiogenic plasma cytokines and decrease of tumor blood flow as measured by DCE-MRI are supportive of the antiangiogenic activity of regorafenib in pts with advanced CRC. Albeit the small number of pts analyzed, KRAS status was not predictive for clinical benefit as measured by PFS.

Disclosure: O. Christensen: Employee of Bayer HealthCare Pharmaceuticals

M. Jeffers: Employee of Bayer HealthCare Pharmaceuticals (Bayer is developing Regorafenib)

J. Krätzschmar: Employee of Bayer Schering Pharma AG

All other authors have declared no conflicts of interest.

620P IDENTIFICATION OF PREDICTIVE BIOMARKERS FOR INDIVIDUAL RESPONSE TO MFOLFOX6 IN COLORECTAL CANCER PATIENTS

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Background: The incorporation of molecular targeting agents such as bevacizumab, cetuximub, and panitumumab, into cytotoxic chemotherapeutic regimens has increased survival in colorectal cancer patients, and provided a promising means of individualization of these therapies. Even so, the clinical efficacy and toxicity of the basic regimens, such as FOLFIRI and FOLFOX, remain unpredictable. Molecular indicators of individual response to the basic regimens are urgently required.

Methods: This prospective study was conducted to determine potent predictive markers of individual response to mFOLFOX6, in terms of efficacy and toxicity. Chemo-naive patients with stage IV colorectal cancer were eligible for this trial after palliative operation, and received mFLOFOX6 treatment. Along with KRAS-mutational analysis in tumor, expression analysis in tumor and genotyping were performed for 9 possible marker genes-DPYD, TYMS, ERCC1, ERCC2, XRCC1, GSTP1, EGFR, VEGF, and TNFRSF1B-. Microarray analysis was also performed to identify novel prediction marker genes closely correlative with response to mFOLFOX6.

Results: Fifty pts received a total of 424 treatment cycles. Overall response rate was 60.4% (1CR and 28 PRs), and median overall and progression survival were 930 days and 234 days, respectively. The most common grade 3/4 toxicities were neutropenia (40%), vomiting (6%), anemia, leucopenia, and neuropathy: sensory (DEB-NTC; 4%). The therapeutic response was not related to tumoral KRAS mutational status at all, and no genotype-toxicity association was observed. However, TYMS expression in tumor was highly correlative with the best tumor response (P=0.039) and overall survival was significantly better in patients with low ERCC2 expression (P=0.039). Furthermore, microarray analyses demonstrated that another 14 genes including RNF145, PEPD and IFITM1 were more correlative with tumor response than TYMS and ERCC2 in the expression levels.

Conclusions: Expression of ERCC2, TYMS, and newly identified 14 genes would be predictive for individual response to mFOLFOX6. A study to validate their predictive values is now going on, along with research for the functional roles of the selected 14 genes.

Disclosure: M. Nishiyama: corporate-sponsored research: Yakult Honsha Co. Ltd

All other authors have declared no conflicts of interest.

621P TITLE: INTERMITTENT VERSUS CONTINUOUS ERLOTINIB WITH CONCOMITANT MODIFIED 'XELOX' (Q3W) IN FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (MCRC)

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Purpose: Erlotinib (EGFR tyrosine kinase inhibitor, TKI) has promising activity when combined with capecitabine (Xe) and oxaliplatin (Ox) ('XELOX') in the 2nd line therapy of mCRC. There is no data on relationship between KRAS status and response to EGFR TKI in mCRC. Preclinical data suggest sequence-dependent synergism between EGFR TKI and fluoropyrimidines, and we therefore evaluated the feasibility of combining erlotinib with XELOX in 1st-line therapy of mCRC.

Method: Chinese patients (pts) with untreated mCRC were randomized to Arm A: Continuous erlotinib (100mg daily, D1-21), Xe 825mg/m(2) bd on D1-14, and Ox 130mg/m(2) D1, q3wk; or, Arm B: Intermittent erlotinib 150mg on alternate days on D1-14, then daily from D15-21, with Xe 750mg/m(2) bd on D1-14, and Ox 130mg/m(2) D1), q3wk. Primary endpoint was response rate (RR). Archived tumors were retrieved retrospectively for KRAS analysis.

Result: 58 pts were randomized (29pts in each arm) in a single institution from Nov 2007 to Nov 2009. Baseline characteristics: median age 56 yrs, 63% male, 74% had prior surgery. Both arms had similar characteristics, except more pts in Arm B had prior adjuvant chemotherapy (p=0.02). Overall RR was 58.6% in Arm B (17/29pts) and 41% in Arm A (12/29 pts, p=0.18, chi-square). For drug compliance: median no. of cycles were 5 (Arm A) and 7 (Arm B); no. of pts who had > 8 cycles were 9 (31%, Arm A) and 12 (41%, Arm B); dose interruptions were required in similar no. of pts in Arm A and B. For toxicity: 14 pts (48%) in each arm had Gr 3-4 toxicities. 1 pt in Arm B died of metabolic acidosis from probable abdominal sepsis. Gr 3-4 thrombocytopenia was more common in Arm A (5 pts, 17%) than Arm B (2 pts, 7%, p = 0.6). Gr 2-3 hyperbilirubinemia was more common in Arm B (11 pts, 34%) than Arm A (5 pts, 17%). Gr 2-3 sensory neuropathy was more common in Arm B (10pts, 34%) than Arm A (3 pts, 10%).

Conclusion: Preliminary analysis suggests that pts on intermittent erlotinib with XELOX had higher RR and incidence of hyperbilirubinemia and sensory neuropathy. Data on KRAS status will be presented.

Disclosure: B. Ma: I am on research grant from Novartis and consultancy with Astra Zeneca.

All other authors have declared no conflicts of interest.

622P COST COMPARISON: CAPECITABINE + OXALIPLATIN (XELOX) VS 5-FU/LV + OXALIPLATIN (FOLFOX4) IN THE ADJUVANT TREATMENT OF PATIENTS WITH COLON CANCER (ACC)

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Background: FOLFOX4 has been the chemotherapy (ctx) of choice for patients with stage III colon cancer. Recently, the international NO16968 study reported results confirming the efficacy of XELOX in this setting, and evidence suggests that both regimens have at least equivalent efficacy. The relative attractiveness of these regimens to providers, patients and payers will depend on medical resource utilization (MRU). This analysis compared the MRU and related costs required to treat an average aCC patient with either XELOX or FOLFOX4 from the Swiss healthcare system perspective.

Methods: In the absence of a direct comparison, detailed MRU data collected for XELOX from study NO16968 (aCC) and for FOLFOX4 from study NO16966 (metastatic colorectal cancer) were analyzed. Since the FOLFOX4 regimen is the same in both indications, MRU data from NO16966 were considered valid proxies for an aCC patient. MRU categories considered were hospitalizations due to adverse events (AEs), ambulatory encounters due to AEs and other reasons, AE medication and central venous access (CVA) placements. Ctx drug and administration costs were considered as per protocol. Unit costs were derived from official tariffs (Spezialitätenliste, Tarmed 2010). Total costs while on treatment (24 weeks) for an average patient with aCC were compared.

Results: The cost comparison shows that XELOX is cost saving vs FOLFOX4 with an average cost reduction per patient of CHF 8883. This cost saving is due to the lower administration costs experienced in the XELOX arm through fewer administrations per cycle and longer cycle length (21 vs 14 days) vs FOLFOX4.

Cost category	XELOX	FOLFOX4	Δ
	Cost in CHF		
Ctx drugs	21066	18948	2118
Ctx administration	5592	14904	–9312
Hospitalization (AEs)	2754	2510	244
Ambulatory encounter (AEs; other)	273	304	–31
AE medication	367	539	–172
CVA	908	2638	–1730
Total	30960	39843	–8883

Conclusion: XELOX appears to be a cost-saving alternative to FOLFOX4 in aCC from a Swiss healthcare system perspective, assuming equivalent efficacy for the two regimens. Considering the high incidence of colon cancer, substantial overall savings may be realized by routine use of XELOX in this indication.

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A. Urspruch: Employee of F.Hoffmann- La Roche, who sponsored the research No other relationships, no stocks;K. Hieke: Klaus Hieke worked as a consultant for Hoffmann-La Roche Ltd

All other authors have declared no conflicts of interest.

623P META-ANALYSIS OF THE VALIDITY OF PROGRESSION-FREE SURVIVAL AS A SURROGATE ENDPOINT FOR OVERALL SURVIVAL IN METASTATIC COLORECTAL CANCER TRIALS

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Background: The validity of progression-free survival (PFS) as a surrogate endpoint for overall survival (OS) in metastatic colorectal cancer (mCRC) trials has been studied extensively, but primarily in first-line treatment (for example, Buyse et al. J Clin Oncol. 2007;25:5218-5224 and Saad et al. Ann Oncol. 2010;21:7-12. Epub 2009 Nov 9). We sought to confirm and extend this research by investigating the influence of such factors as line of therapy on the relationship between OS and PFS in mCRC treatment trials.

Methods: In a systematic literature review, mCRC phase 2 and 3 trials that presented OS and PFS (or time-to-progression) results were eligible. Correlation between these endpoints was estimated by single treatment arm and by study. Treatment effect in each study was defined as the ratio of the median time to event (either OS or PFS) in the two treatment arms. Meta-regression analyses were conducted using least squares meta-regression models weighted by study sample size. Statistically significant factors were used to create subgroup analyses.

Results: A total of 66 articles met the initial search criteria and 62 were included in the analysis (total of 23,527 patients). High positive correlation was found between the median PFS and median OS within treatment arms [Pearson coefficient 0.87, (95% confidence interval [CI] 0.82-0.91)] and also between the treatment effects for OS and PFS by study [0.69, (0.53-0.80)]. The regression equation for the relationship between treatment effects was: OS Effect = 0.60 + 0.41*PFS Effect. Thus, a 1-unit increase in PFS treatment effect predicts a 0.41 unit increase in OS treatment effect. Line of therapy was determined to be a significant factor with the R^2 higher for first-line ($R^2 = 0.54$) compared to second-line studies ($R^2 = 0.38$).

Conclusions: Our results demonstrate a strong and consistent linear relationship between treatment effects for PFS and OS. The relationship appears to be stronger in first-line studies but is still evident in second-line studies.

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624P ANALYSIS OF NEUROSENSORY ADVERSE EVENTS (NSAES) INDUCED BY FOLFOX4 TREATMENT IN ADVANCED/ RECURRENT OR ADJUVANT COLORECTAL CANCER IN ASIAN AND WESTERN PATIENTS (PTS)

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Background: FOLFOX4 is a standard regimen for the treatment of advanced/recurrent and adjuvant colorectal cancer. In order to support Japanese adjuvant indication, NSAEs were evaluated in both Asian and Western Pts in 6 FOLFOX4 studies.

Materials and methods: A total of 3359 colorectal cancer Pts, 1515 Asian and 1844 Western, treated by FOLFOX4 were included from 2 Asian [J-PMS (Jpn Post Marketing Surveillance) and adjuvant MASCOT] and 4 Western [de Gramont 1st line phase III (EFC2962), Goldberg 1st line phase III (N9741), Rothenberg 2nd line phase III (EFC4584) and adjuvant MOSAIC] studies. NSAEs were graded by DEB-NTC (J-PMS), NCI-CTC ver. 1 (EFC2962, MOSAIC) or ver. 2 (MASCOT, N9741, EFC4584) scales, re-coded by MedDRA ver 9.0, and analyzed by SAS® ver 8.1.

Results: Pts received FOLFOX4 for 6 - 12 cycles over 16 - 28 weeks. Median dose intensities of L-OHP, bolus and infusion 5-FU were 33 - 36, 297 - 338 and 467 - 510 mg/m^2/wk, respectively. In both populations, NSAE was one of the most frequent grade ≥1 AEs (50.6 - 92.1%), and grade ≥3 AEs were reported in 1.9 - 18.7%. The incidence increased with increase in L-OHP cumulative doses (CD). The CD⊂10, that induced grade ≥3 NSAEs in 10% Pts calculated by Kaplan-Meier method, were higher in Asian Pts (1526 mg/m^2 and NR) than in Western Pts (805 - 832 mg/m^2). All Pts who experienced grade-3 NSAEs in MASCOT recovered to grade 2 or less within 12 months of follow-up, and 96% of grade-3 Pts in MOSAIC. Analysis of correlation between NSAEs and demographic/baseline characteristics by Fisher's exact test and logistic regression showed no significant trend.

Conclusions: There was a trend toward reduced NSAEs (grade ≥3) among Asian Pts as compared with Western Pts.

	J-PMS		MASCOT	EFC2962	N9741	EFC4584	MOSAIC
Line	1st	≥2nd	Adju.	1st	1st	2nd	Adju.
Pt No.	222	1134	159	209	259	268	1108
Median cycles	8	6	12*	12	10	7	12*
OHP CD (mg/m^2)	657	500	967	839	765	589	888
Grade≥1 NSAE (%)	58.6	50.6	83.6	82.8	79.9	75.0	92.1
Grade≥3 NSAE (%)	2.7	1.9	4.4	18.7	18.1	9.3	12.4
OHP CD⊂10 (mg/m^2)	1526**		NR***	805	827	821	832

* Max 12 cycles; ** n=1356; *** Not reached

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A. De Gramont: Consultant or Advisory Role: sanofi-aventis Yakult Honsha Co., Ltd. Honoraria: sanofi-aventis Yakult Honsha Co., Ltd. No other conflict of interest

R.M. Goldberg: Consulting Payments: sanofi-aventis Genentech Amgen BMS/ ImClone Research Funding: sanofi-aventis Genentech Amgen No other conflict of interest

M.L. Rothenberg: Consultant or Advisory Role: sanofi-aventis Research Funding: sanofi-aventis No other conflict of interest

T. André: Honoraria: sanofi-aventis Baxter No other conflict of interest

S. Brienza: Employment: Employee of Debiopharm S.A. No other conflict of interest

All other authors have declared no conflicts of interest.

625P SIGNIFICANT IMPACT OF HER2/NEU,BCL-2 AND P53 OVEREXPRESSION ON SURVIVAL IN COLORECTAL CANCER (USING TISSUE MICROARRAY)

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Background: Widespread genetic mutations in colorectal carcinogenesis exist on chromosome 17. Her-2/neu gene and the tumor suppressor gene p53 are both located on this chromosome. Bcl-2 protein prolongs survival of a variety of cells by blocking apoptosis. The aim of this study is to evaluate the relationship between the overexpression of p53, bcl-2 and her-2/neu protein markers and the clinico-pathologic characteristics of CRC, and their influence on survival rates specially in Duke B CRC

Patients and methods: One hundred and forty cases of CRC had paraffin blocks with representative tissue, and sufficient follow-up data. They were arrayed and evaluated for protein marker expression using tissue microarray (TMA).

Results: her-2/neu, p53 and bcl-2 positive were positive in 10%, 34% and 26% of the patients respectively. None of the examined clinico-pathologic factors had a significant relation with her-2/neu overexpression. Patients with +ve bcl-2 had a significantly higher mean age (52.4±13.3years) compared to 45.4±14.4 years for bcl-2 negative patients, p=0.03. Positive p53 was overexpressed in 20/44 (45.5%), 6/17 (35%), 9/43 (21%) cases of the colon, recto-sigmoid, and rectal sites, respectively, p=0.05. For the whole population, p53 overexpression had a significantly lower disease-free survival (DFS). For patients with Dukes' stage B, overexpression of p53 protein had a significant reduced overall survival (OS) p=0.04, metastasis free survival (MFS) p=0.004, and DFS p=0.01 rates. Her-2/neu overexpression worsened the OS rate significantly, p=0.04.

Conclusion: This study recommends the application of TMA technique for its economic importance and reliable quick throughput. The results from this study also suggest that overexpression of p53, bcl-2, and her-2/neu protein markers appear to be useful in selecting a group of CRC patients with a worse prognosis and constitute potential candidates for adjuvant therapy.

Disclosure: All authors have declared no conflicts of interest.

626P THROMBOCYTOSIS AS A PREDICTIVE AND PROGNOSTIC MARKER IN ADVANCED COLORECTAL CANCER (ACRC): RESULTS OF THE MRC COIN TRIAL EXPLORED.

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Background: Simple and reliable biomarkers for cancer therapy have the potential to make huge differences to individual patient care. COIN randomised 1630 pts. with previously untreated aCRC to continuous (arm A) or intermittent (arm C) chemotherapy. It identified a non-significant difference in OS of 1.5 mths (PPA) in favour of continuous therapy at the expense of 2.3 mths of extra time on treatment. Here we explore sub-group analyses to predict those individuals most likely to benefit from continuous therapy.

Methods: A Cox proportional-hazards model was fitted separately for patient, pathological and biological covariates to predict OS in the PPA population. In each case, treatment arm, the predictive factor, and a treatment-predictive factor interaction term were entered into the model. Interaction tests were carried out using likelihood-ratio tests of the null hypothesis that the interaction coefficient is zero.

Results: A baseline platelet level >400/nL identified a group of patients (28%) with worse prognosis and with a significant survival detriment in using intermittent therapy, test for interaction: HR=1.65 (95% CI 1.19 to 2.28), p=0.003. Patients. with raised baseline platelets are more likely to be male, <65 yo, and have WHO PS 1+, primary tumour in the colon, unresected primary, synchronous metastases, liver metastases, peritoneal metastases. There is an increased incidence of pain and vomiting in those with raised platelets, which appears better controlled on continuous therapy. In Arm A, raised platelet count is not associated with increased pain: G1+: 66% vs 71% (p=0.282). In Arm C, raised platelet count is significantly associated with increased pain: G1+: 72% vs 86% (p=0.001).

NRAS, KRAS and BRAF mutation status were not associated with platelet level. Further analyses will be presented in terms of biological data QoL and toxicity.

Discussion: This simple routinely performed biomarker can identify a subset of patients who do much less well with intermittent chemotherapy. In contrast, those three quarters of patients in this study with normal platelets at randomisation suffered no loss in overall survival and reaped all the benefits of chemotherapy free intervals.

Disclosure: All authors have declared no conflicts of interest.

627P NATURAL HISTORY OF MALIGNANT BONE DISEASE IN COLORECTAL CANCER: FINAL RESULTS OF A LARGE ITALIAN "BONE METASTASES" SURVEY

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Introduction: bone metastases are an emerging clinical problem in colorectal cancer patients probably related to survival increase. There are no data in literature about the natural history of bone disease in colorectal cancer. We report the final data of a large Italian multicenter survey.

Methods: 264 colorectal cancer patients with evidence of bone metastases have been included in the study. All patients were died due to cancer at the moment of the study inclusion. Clinico-pathological data, data on survival, Skeletal Related Events (SRE) data and skeletal related therapies have been collected in a master data base and statistically analyzed.

Results: the median time to bone metastases appearance was 11 mths (4.67 – 13.06); grading of primary tumor (p: 0.0001) and the appearance of visceral metastases (p: 0.0001) resulted predictive of skeletal disease. Mucinous histotype showed a trend of higher risk of bone metastases appearance (p: 0.069). No site, neither T or N correlated with bone progression. The median time to first SRE was 2 mths (1.04 – 3.45). The osteolytic nature of bone metastases correlated with time to first SRE (p: 0.0001). No cancer treatment or single versus multiple bone metastases correlated with median time to first SRE. The median survival after skeletal progression was 7 mths (5.75 – 8.704). Osteolytic nature of metastases (7 months versus 21 months) (p: 0.008) and multiple sites of bone metastases (p: 0.004) correlated with median survival after skeletal progression. The median survival after first SRE was 4.5 mths (3.43 – 6.13).

Conclusions: complete results of statistical analysis will be presented during the meeting. The present survey is the first descriptive study concerning the natural history of bone disease in colorectal cancer patients.

Disclosure: All authors have declared no conflicts of interest.

628P EFFICACY OF ZOLEDRONIC ACID IN PATIENTS WITH COLORECTAL CANCER METASTATIC TO BONE

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Introduction: bone metastases are an emerging clinical problem in colorectal cancer patients probably related to survival increase. There are no data in literature about the role of BPs in the treatment of bone disease from colorectal cancer. We present the final data of a large Italian multicenter retrospective analysis.

Methods: 264 colorectal cancer patients with occurrence of bone metastases have been included in the study. All patients were died due to cancer at the moment of the study inclusion. Patients characteristics, Skeletal Related Events (SRE) data and median survival after bone metastases appearance have been collected in a master data base and statistically analyzed. The primary efficacy endpoint was time to first SRE; secondary endpoint was median survival. 31 patients have been analysed as control group.

Results: In 107 patients bisphosphonates data were not available. A total of 157 patients have included for zoledronic efficacy analysis. A total of 126 patients received zoledronic acid (4 mg) via a 15-minute infusion every 4 weeks until performance status worsening or death.. The median time to first SRE in the whole population was 2 mths (1.04 – 3.45). The median time to first SRE in the zoledronic treated patients was 3.168 mths (0.49 – 2.19) compared with 1.71 mths (0.41 – 0.90) in the control group (p: 0.009). The median survival after skeletal progression was 7 mths (5.75 – 8.704). The median survival in the zoledronic treated group was 10 mths (8.08 – 11.91) compared with 6 mths (4.45 – 7.54) (p: 0.161).

Conclusions: complete results of statistical analysis will be presented during the meeting. The present analysis represent the efficacy demonstration of a bisphosphonate in bone metastases from colorectal cancer patients

Disclosure: All authors have declared no conflicts of interest.

629P PRELIMINARY RESULTS FROM THE SOUTH AUSTRALIAN (SA) CLINICAL REGISTRY FOR ADVANCED COLORECTAL CANCER (CRC) ASSESSING THE IMPACT OF AGE AND CHOICE OF CHEMOTHERAPY ON OUTCOME

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Aims: The SA Clinical Registry for Advanced Colorectal Cancer aims to encompass all patients in SA who have been diagnosed with metastatic CRC (mCRC). We report here outcomes, assessing the difference in treatment patterns for those <70 yrs with those ≥70 yrs and outcome based on initial choice of chemotherapy (CT).

Methods: All patients diagnosed with mCRC after 1/2/2006 were eligible to be included. For this analysis patients receiving CT were assessed by choice of single or combination CT (CCT) and by age (<70 yrs and ≥70 yrs). Disease-specific survival data was assessed using Kaplan-Meier product moment estimates.

Results: 1544 patients with mCRC have been entered. Mean age 71 yrs (range 17.4-105.4yrs). 822 (52.6%) patients had some form of CT for mCRC; median age 68 yrs, compared to median age for no CT of 79 yrs (28% of patients <70 yrs and 59% ≥70 yrs did not receive CT). Of those patients who received CT, the characteristics of those <70 yrs and ≥70 yrs were well balanced for gender, location of primary, hepatic only

metastases, and rates of hepatic and lung resection. 81% and 51% of those <70 yrs and ≥70 yrs respectively received CCT first-line, and 47% and 19% received second-line CT, while 35% and 11% received third-line CT. 30% of patients <70 yrs received at least one line of treatment containing EGFR or VEGFR targeted therapy and 14% ≥70 yrs. Median survival of patients <70 yrs and ≥70 yrs receiving CT was 24.4 months and 20.4 months respectively (p=0.2) and 21.4 months and 24.8 months for those who also received targeted therapy. Median survival for patients receiving first-line single agent fluoropyrimidine was 16 mths (n=249, med age 74yrs) compared to first-line CCT 26 months (n=558, med age 65yrs) (p=0.001, HR 1.74) and using cox regression analysis age was not an independent predictor for survival.

Conclusions: Age appears to impact on the initial CT choice, with the majority of patients <70 yrs receiving first-line CCT whereas nearly 50% of those ≥70 yrs received single agent therapy. Comorbidity may have impacted on treatment decisions, however, survival appears to be better in those treated with first-line CCT and should still be considered in the older patient.

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All other authors have declared no conflicts of interest.

630P PATIENTS NOT RECEIVING SYSTEMIC THERAPY FOR METASTATIC COLORECTAL CANCER – WHAT ARE THE DRIVERS AND WHAT ARE THE OUTCOMES?

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Background: Despite major advances in the systemic therapy of metastatic colorectal cancer (mCRC), leading to improved symptom control and life expectancy, some pts still do not receive any treatment. Analyses of this pt population are critical to understanding the reasons that treatment may not be pursued, the appropriateness of this decision and the ultimate impact on survival outcomes.

Methods: We examined a prospective, comprehensive database at 4 hospitals for detail regarding patients diagnosed with mCRC between January 2003 and December 2009, focusing on the patients that were not treated and their survival outcomes.

Results: 445 pts (60% male, 40% female) with metastatic disease were identified. Preliminary analyses revealed that 221 pts (49.6%) had chemotherapy initiated at diagnosis and 62 pts (14%) had later treatment after an initial watch and wait approach. Of the pts that never received treatment (n=162, 36.4%), for 153 (94%) this decision was made at diagnosis, with only 9 pts (6%) that initially undertook a wait and watch approach never receiving treatment. Pts for whom the decision not to treat was made at diagnosis, were significantly ($p < 0.05$) older (median age 71.4 yrs vs. 63.6 years for pts treated immediately) and with a worse performance status (PS) (8.33% ECOG >2 vs. 1.61% of treated pts). Sites of disease, presence or absence of symptoms and co-morbidity as calculated by the Charlson's index did not significantly impact on treatment decisions. Of the untreated pts, the most frequently documented reason for not undergoing treatment was poor PS (50.8%) followed by comorbidities (41.5%) and/or age (16.7%). Data related to the median survival of untreated versus treated pts will be presented.

Conclusions: A significant proportion of patients with metastatic colorectal cancer do not receive any systemic therapy, a decision that is usually made at the time of diagnosis. Most patients undertaking an initial watch and wait approach are ultimately treated. Poor PS, co-morbidity and advanced age are the dominant reasons that pts do not receive treatment.

Disclosure: All authors have declared no conflicts of interest.

631P SHOULD THE PRIMARY TUMOR BE RESECTED IN PATIENTS WITH UNRESECTABLE SYNCHRONOUS METASTASIS OF COLORECTAL CANCER ? PROGNOSTIC RETROSPECTIVE MULTICENTRIC STUDY OF 128 PATIENTS

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Introduction: Indication of primary tumor resection remains controversial in patients (pts) with asymptomatic colorectal cancer (CRC) and unresectable synchronous metastasis. The aim of this study was to compare survival of patients with metastatic CRC who underwent elective resection of the primary tumor to those who did not.

Patients and methods: Data of 275 consecutive pts from 5 centres treated with palliative first line chemotherapy for metastatic CRC between June 2004 and June 2008, were retrospectively reviewed. Demographic, clinical, tumor-related, and chemotherapy-related variables were collected in 128 pts with synchronous metastases and good performance status (ECOG 0 or 1). Overall survival (OS) was calculated from the first date infusion of chemotherapy to death or last follow-up. Survival analyses were performed using the Log-Rank test and the Cox Model.

Results: The 128 pts were male in 72% (92/128). Median age was 63 years old (38-88). 67% (86/128) of patients underwent primary resection. Characteristics for pts with tumor's resection/non-resection are as follow : 66(79%)/24(57%) colonic tumors (p=0.01), 24(28%)/12(29%) > 1 metastatic site (p>0.05), 61(71%)/29(69%) > 1 palliative chemotherapy's lines (p>0.05), 43(50%)/23(55%) doublet chemotherapy regimens for the first-line chemotherapy (p>0.05). Median follow-up was 22/17 months (mo) for 61(71%) / 39(93%) pts died. Median OS was longer if primary tumor resection was performed (24.8 mo (CI95%[17.3-29.7]) vs 17.5 mo (CI95%[12.5-21.2]); p<0.01). In multivariate analysis, OS was significantly improved for patient with primary tumor resection (HR 2.2; CI 95%[1.3-3.8]; p=0.02) whatever number of metastatic sites, number of palliative chemotherapy's lines and type of the first-line chemotherapy.

Conclusion: Primary tumor resection seems to improve overall survival in patients with synchronous CRC metastases and good performance status. A prospective randomized trial integrating the quality-of-life factor should be organized.

Disclosure: All authors have declared no conflicts of interest.

632P SURVIVAL AFTER SURGICAL RESECTION OF HEPATIC METASTASES FROM COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Purpose: To summarize studies of survival after resection of colorectal cancer liver metastases (CLM).

Methods: We reviewed articles published 1999–2009 in English of studies with ≥100 patients who underwent liver resections for CLM with ≥24 months of follow-up. This updates a previous review of studies published 1982-2000[1]. Results were summarized for post-operative mortality and morbidity, health care resource utilization costs, quality of life, and clinical guidelines. Seven prognostic factors of mortality were considered in a meta-analysis: grade, tumor size, extrahepatic disease, number of hepatic metastases, number of positive lymph nodes, carcinoembryonic antigen level, and positive resection margin.

Results: 142 studies met the inclusion criteria, nine of which were included in the previous review[1]; seven further studies were identified that reported on clinical guidelines. Post-operative mortality ranged from 0-4%. The three most common post-operative fatal complications were hepatic failure (23.8%), sepsis (15.5%), and myocardial infarction (14.3%). Post-operative blood transfusions occurred in 36% of patients, a reduction from 64.3% reported previously[1]. Five-year survival varied from 16%-71% (mean 39%, median 38%), an improvement from the mean of 30-35% previously reported[1]. Forty studies were included in the meta-analysis: hazard ratios (and 95% confidence intervals) were: node positive primary [1.5 (1.4-1.7); p-heterogeneity (p⊂h)=0.606; number of studies (n)=13]; extra-hepatic disease [1.4 (1.2-1.7); p⊂h=0.056; n=6)]; and poorly differentiated tumor [1.3 (1.1-1.5), p⊂h=0.059; n=4]. Significant heterogeneity across studies precluded analysis of other factors. Country specific clinical guidelines were generally similar.

Conclusions: Observed 5-year survival after liver resections for CLM was higher in this review compared to a similar review of studies published before 2001[1]. Further work is ongoing to investigate these differences and quantify the effect of prognostic factors on survival. 1. Simmonds P et al. Surgical resection of hepatic metastases from colorectal cancer: A systematic review of published studies. Br J Cancer 2006; 94: 982-99.

Disclosure: A. Taylor: I work for Amgen and have Amgen stock ownership; G. Kanas, L. Morimoto, M. Kelsh and F. Mowat: Exponent has received funding to carry out this corporate sponsored research from Amgen; W. Langeberg: I work for Amgen and have stock ownership in Amgen; M. Choti: I have carried out some consultation work for Sanofi-Aventis and Genentech-Roche. All other authors have declared no conflicts of interest.

633P ANALYSIS OF OVERALL SURVIVAL AMONG PATIENTS WITH METASTATIC COLORECTAL CANCER, WITH AND WITHOUT UNDERGOING ELECTIVE COLECTOMY

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Analysis of overall survival among patients with metastatic colorectal cancer, with and without undergoing elective colectomy

Introduction: Controversy exists regarding the management of metastatic colorectal cancer. Palliative resection of the primary tumor has become established for patients presenting uncontrollable bleeding, total intestinal obstruction or perforation.The real benefit from resecting the primary tumor in asymptomatic patients remained undefined.

Objectives: Evaluate overall survival among patients with metastatic colorectal cancer who underwent elective surgery to resect the primary tumor, in comparison with patients who did not undergo this procedure, along with their prognostic, demographic and clinical factors.

Methods: Retrospective cohort study in which 203 patients with metastatic colorectal cancer at Barretos Hospital. Demographic, clinical and treatment variables were gathered. Descriptive analysis was performed on the data. For the survival analysis, the Kaplan-Meier product-limit estimator was used. To compare the curves, the log-rank test was used. Variables that presented descriptive levels lower than 20% were entered into the Cox multiple regression model.

Results: The 12-month overall survival(OS) among the patients who underwent elective colectomy was 66,4%, 36-month OS was 26,4% and 60-month OS was 16,2% The patients who did not undergo surgery had a 12-month OS of 25,1%,36- OS of 1,3% and 60-month OS of 1,3% (p<0,001). Independent prognostic factors were: not undergoing the colectomy procedure; not undergoing resection of metastasis; and not undergoing chemotherapy, adjusted according to the patients' performance status.

Conclusion: The results from our study suggest that asymptomatic metastatic patients who underwent elective colectomy presented favorable outcomes with greater overall survival. The other independent factors that led to a better prognosis were resection of the metastatic disease and implementation of chemotherapy, adjusted for good clinical conditions (performance status). The benefit regarding survival was directly proportional to the number of treatments that patients were able to undergo.

Disclosure: All authors have declared no conflicts of interest.

634P RIPK1 POLYMORPHISM AS PROGNOSTIC MARKER FOR SURVIVAL IN PATIENTS WITH COLORECTAL CANCER AFTER COMPLETE RESECTION

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Since apoptosis plays a key role in cancer progression, the present study analyzed the polymorphisms of apoptosis-related genes and their impact on survival after curative resection in patients with colorectal cancer. Three hundred and ninety seven patients were enrolled in the present study. The genomic DNA was extracted from fresh colorectal mucosal tissue, and 15 SNPs of 12 apoptosis-related genes determined using a Sequenom MassARRAY system. During the median follow-up of 41.6 (range, 0.7-85.5) months, 80 relapses and 67 deaths occurred. Among the target polymorphisms, FAS rs10788624 and rs1800682 in a recessive model of the minor allele and RIPK1 rs2272990 in a dominant model of the A allele were associated with survival in a log-rank test. Moreover, the GA+AA genotype of RIPK1 +83G>A (rs2272990) was significantly correlated with a worse disease-free and disease-specific survival when compared to the GG genotype (hazard ratio [HR] = 1.810; 95% confidence interval [CI] = 1.108 - 2.959; p=0.018 and HR = 2.372; 95% CI = 1.302 - 4.321; p=0.005, respectively) in a multivariate survival analysis. RIPK1 polymorphism can be considered as a possible prognostic marker for survival after curative resection in patients with colorectal cancer.

Disclosure: All authors have declared no conflicts of interest.

635P RESECTION OF COLORECTAL CANCER (CRC) METASTASES AFTER BEVACIZUMAB (BV) TREATMENT FOR 1ST-LINE THERAPY: RESULTS OF THE ETNA COHORT STUDY.

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BV associated with chemotherapy has been demonstrated to improve overall survival (OS) in metastatic CRC (mCRC). This allows to consider secondary resection of metastases for the initially unresectable mCRC.

ETNA is a cohort study conducted in 28 French centers. It included patients (pts) initiating BV from Jan 2006 to Dec 2007. Those treated in 1st-line therapy for mCRC were followed for 24 months. Effectiveness for pts with secondary resection of metastases and curative intent is presented here.

A total of 411 pts had 1st-line therapy with BV for mCRC: 347 were analyzable after 24 months of follow-up, and 67 (19.3%) had metastasis resection (pts operated, oPts). oPts main baseline characteristics were: mean age: 61.6 y, male: 46.3%, ECOG 0-1: 91.0% and one metastatic site: 58.2%; those of not operated pts (noPts) were: mean age: 64.0 y, male: 60.0%, ECOG 0-1: 77.5% and one metastatic site: 55.7%. Among the oPts, resection site was: liver n=44, lung n=10, other n=20. Results of surgery available for 56 oPts were: R0-R1: 85.7%, R2: 14.3%. The median time from BV initiation to 1st resection was 207 days. For oPts, BV was mainly associated with irinotecan-based regimens (97.0%) and with FOLFOX regimens (3.0%); for noPts it was: FOLFIRI: 83.6%, XELIRI: 2.9%, FOLFOX: 10.7%, XELOX: 2.5% and FOLFIRINOX: 0.4%. Objective response rate was 85.1% including 32.8% complete response (vs 49.3% and 5.4% for noPts), stable disease 14.9% (vs 30.0%) and absence of progressive disease (vs 17.1%). Median duration of BV treatment was 6.9 months and of 1st-line therapy was 14.3 months (vs 5.0 and 8.3 months for noPts). Median PFS was 13.6 months for oPts, the 1-yr OS rate was 94.0% (95%CI 84.9-97.7) and the 2-yr OS rate was 81.7% (95%CI 70.0-89.2) (vs for noPts: median PFS 9.0 months, 1-yr OS rate 75.2% [95%CI 69.6-79.8] and the 2-yr OS rate 44.5% [95%CI 38.5-50.4]). Median OS was not reached for oPts and was 21.9 months for noPts.

For pts treated by BV in a real-life setting, secondary resection of mCRC for initially unresectable metastases was possible for 19% of pts with 85.7% R0-R1. Evaluation of morbidity and longer follow-up will allow the real long-term benefit to be studied.

Disclosure: All authors have declared no conflicts of interest.

636P FUFIRI OR MIROX FOR FIRST-LINE TREATMENT IN METASTATIC COLORECTAL CANCER (MCRC) AND SECONDARY RESECTION OF LIVER METASTASIS: A POST-HOC ANALYSIS OF TUMOR RESPONSE AND OVERALL SURVIVAL IN THE FIRE-TRIAL

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Background: Chemotherapy in metastatic colorectal cancer (mCRC) can downsize colorectal liver metastasis (CLM) for curative secondary resection. We evaluated downsizing and survival of FUFIRI and mIROX treatment in non-selected pts in this setting.

Patients and methods: Data from a phase III, randomized, multicenter trial with 479 pts treated with FUFIRI (irinotecan 80 mg/m^2, 5-FU 2000 mg/m^2, folinic acid 500 mg/m^2 weekly) or mIROX (irinotecan 80 mg/m^2 plus oxaliplatin 85 mg/m^2 weekly) applied on days 1, 15, and 29 of a 7-week cycle were evaluated. Assessment of the largest hepatic lesion was performed at the time of randomization and before surgery.

Results: Secondary liver resection was performed in 23 pts of the FUFIRI arm (9.7%) and 15 patients of the mIROX arm (6.2%) (p= 0.179). Total resection rate of the study was 7.9% (38/479). R0-resection could be realized in 29 cases (18 vs. 11, FUFIRI vs. mIROX, p=0.169). Resection rates in the subgroup of liver-only pts (248/479, 51.8%) were 20.2% (FUFIRI) and 11.2% (mIROX) (p=0.050). R0-resections 15.8% and 8.2%, (p=0.064). In both groups highly significant downsizing of liver metastasis with 33.3% reduction of length, 35.0% reduction in width and 57.6% reduction of surface could be achieved (p<0.001). Identical objective response rate (ORR) of 41% could be induced in both regimens but disease control rate (DCR = ORR + SD) was significantly greater in the FUFIRI group (81% vs. 69%, p=0.001). These findings were consistent with results of the liver-only subgroup (87% vs. 67%, p<0.001). Median overall survival (OS) of all 38 resected pts was 45.8 months. One-year-survival and 5-year-survival was 97.4% and 37.1%, respectively.

Conclusion: Both FUFIRI and mIROX treatment showed highly significant size-reduction of colorectal liver metastasis. There was a trend towards a higher resection rate and R0-resections in the liver-only subgroup for FUFIRI-treatment. This trend

may be explained by higher DCR rates in the FUFIRI pts. Patients who underwent hepatic resection showed favorable long-term survival with median OS 45.8 months. and 5-year-survival of 37.1%.

Disclosure: All authors have declared no conflicts of interest.

637P THE ROLE OF PERIOPERATIVE BEVACIZUMAB IN THE MANAGEMENT OF PATIENTS WITH COLORECTAL CANCER AND LIVER METASTASES TREATED WITH LIVER METASTASECTOMY

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Background: Patients with colorectal cancer (CRC) and liver metastases benefit from perioperative chemotherapy (Ch) and liver resection. There is still concern among clinicians of the impact of adding Bevacizumab (B) on liver resection complications.

Patients and methods: This is a single centre retrospective analysis of outcomes of patients with CRC and liver metastases treated with perioperative Ch +/- B followed by liver metastasectomy. Seventy seven patients, 46 males, 31 females, were identified from our prospectively maintained database.

Results: The majority of patients (74%) received Oxaliplatin based Ch. Nearly half of the patients (46%) received B in addition to Ch. Over 70% received systemic treatment pre and post liver resection with the remaining receiving preoperative treatment alone. The median time from neoadjuvant Ch +/- B to liver resection was 62 days (33-181) and the median time between liver resection and adjuvant chemotherapy was 62 days (18-115). The rate of R0 resections was 29/41 (70%) in the Ch and 22/36 (61%) in the Ch/B group (χ^2 0.373, non significant). Postoperative complications developed in 25/41 (61%) patients who received Ch alone and 25/36 (69%) patients who received Ch/B (χ^2 0.604, non significant). Complications observed in the Ch/B group included: liver dysfunction (predominately hyperbilirubinaemia) (17/36=47%), cardiac abnormalities (6/36=16%), infection (5/36=14%), respiratory problems (4/36=11%), wound dehisence (4/36=11%), DVT/PE (2/36=5%), bleeding/haematoma (2/36=5%). No significant association was found between predictive factors (age, gender, performance status, > 4 metastases, size of largest metastasis) and greater benefit with the addition of B in improving PFS or OS. No association was found between time from chemotherapy to surgery and complication rates. Relapse rates were similar in both groups (23/41=56% in Ch vs 18/36=50% in B group) with liver and lung being the commonest sites or recurrence for both groups.

Conclusion: The addition of B to standard chemotherapy does not increase liver resection complication rates. Larger studies are required to determine the impact of the addition of B on survival.

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All other authors have declared no conflicts of interest.

638P LIVER RESECTION PLUS LOCAL DESTRUCTION OF LIVER METASTASES FOR PATIENTS WITH METASTATIC COLORECTAL CANCER

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Introduction: Due to initial wide spread of the disease only 4-15% pts with colorectal liver metastases (CLM) receive radical liver resections and most pts receive only palliative chemotherapy. 5-year overall survival in this group of pts is less than 5%. The aim of our study was to increase overall survival of pts with CLM by the use of liver resection in combination with local destruction methods.

Methods: Retrospective analysis included 527 pts with CLM who had received surgical treatment in 1990-2008. Out of them 496 pts underwent liver resections (liver resection group) and 31 pts - simultaneous liver resections and local destructive methods (combined group) - radiofrequency ablation (11 pts) or cryodestruction (20 pts). Indications for these procedures were localization of lesions near major blood vessels or bile ducts and cases when future remnant liver volume would be less than 25%. Twenty five pts received the following postoperative chemotherapy: FOLFOX (n=13), FU/LV (n=7) or other regimens (n=5). Postoperative complications of the combined group and the liver resection group were compared and overall survival rate in the combined group was calculated.

Results: Median overall survival in the group of liver resection combined with local destruction methods was 26 months, 5-year survival rate was 20.8%. The median blood-loss in the liver resection group was 1450 ml (50.0 – 10000.0 ml). Postsurgical complications occurred in 158 pts (31.9%), 16 pts died (3.2%). Liver failure was the most common complication, developing in 83 pts (16.1%). Bile fistula was second-ranking complication (46 patients, 9.3%). The median blood-loss in the combined group was 1500 ml (400.0 – 4000.0 ml), mortality rate - 3.2% (1 patient), postsurgical complications occurred in 8 cases (25.8%), liver failure – in 3 cases (9.7%) and bile fistula – in 3 cases (9.7%).

Conclusions: Combined treatment for CLM including liver resection and local destruction methods do not increase surgical complications and seem to increase overall survival rate in the group of pts with unrespectable CLM.

Disclosure: All authors have declared no conflicts of interest.

639P TREATMENT FOR RECURRENCE AFTER HEPATECTOMY IN PATIENTS WITH COLORECTAL LIVER METASTASIS

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Aims and patients: This retrospective study was performed with data of 202 patients, who underwent hepatectomy for solitary or multiple liver metastasis from colorectal cancer, to evaluate factors influencing the long-term survival and therapeutic significance for recurrence after initial hepatectomy.

Results: Cumulative 5 and 10 year survival rates after initial hepatectomy were 44.1% and 31.4%, and cumulative 5 and 10 year disease-free survival were 18.3% and 18.3%, respectively. Survival rates were not significantly different among the patients with solitary liver metastasis, those with 2 or 3 metastasis and those with 4 or more metastasis. After diagnosis of recurrence in 153 patients, repeat resection was performed in 73, chemotherapy alone in 36, and best supportive care in 44. Between patients with solitary and pleural liver metastases, overall survival rate was not different but the former had significantly better disease-free survival rate. Also, survival rates after recurrence were not significantly different between those two patients groups. These findings indicate that treatment after recurrence might improve survival in patients with plural liver metastases. In patients who underwent hepatectomy for solitary liver tumor at initial hepatectomy, those eligible for surgical resection for recurrent sites had significantly better survival rates than patients with best supportive care, but not different from patients with chemotherapy alone. In patients with plural metastatic liver tumors at initial hepatectomy, those eligible for surgical resection for recurrent sites had significantly better survival rates than patients with chemotherapy alone and than patients with best supportive care, suggesting that surgical resection provided survival benefit as a therapeutic approach on just patients with pleural liver metastasis at initial hepatectomy than those with solitary liver tumor.

Conclusions: Although high recurrence is inevitable after resection of multiple liver metastases from colorectal cancer, surgical resection after recurrence could promise prognosis equal to solitary liver metastasis for patients with multiple liver metastases at initial hepatectomy.

Disclosure: All authors have declared no conflicts of interest.

640P A RANDOMIZED PHASE III TRIAL OF ADJUVANT CHEMOTHERAPY WITH IRINOTECAN, LEUCOVORIN AND FLUOROURACIL VERSUS LEUCOVORIN AND FLUOROURACIL FOR STAGE II AND III COLON CANCER: A HELLENIC COOPERATIVE ONCOLOGY GROUP STUDY

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Background: Irinotecan (CPT-11), a topoisomerase I inhibitor, is effective when combined with 5-fluorouracil (5FU) and leucovorin (LV) for the treatment of metastatic colorectal cancer. When this study was designed 5FU plus LV was standard adjuvant treatment for colon cancer. We evaluated the efficacy and safety of weekly bolus irinotecan plus 5FU plus LV in the treatment of patients with stage II or III colon cancer.

Methods: The study included 873 eligible patients. The treatment consisted of weekly administration of irinotecan 80 mg/m^2 intravenously (IV), LV 200 mg/m^2 and 5FU 450 mg/m^2 bolus (Arm A) versus LV 200 mg/m^2 and 5FU 500 mg/m^2 IV bolus (Arm B). In Arm A treatments were administered weekly for 4 consecutive weeks, followed by a 2-week rest, for a total of six cycles, while in Arm B treatments were administered weekly for 6 consecutive weeks, followed by a 2-week rest, for a total of four cycles. The primary end-point was disease-free survival (DFS) at 3 years.

Results: There were no differences between the arms in 3-year overall and disease-free survival. With the exception of leucopenia and neutropenia, which were higher in patients in Arm A, there were no significant differences in Grade 3 and 4 toxicities between the two regimens. The most frequently recorded Grade 3/4 toxicity was diarrhea in both treatment arms,

Conclusions: Irinotecan added to weekly bolus 5FU plus LV did not result in improvement in disease-free or overall survival in stage II or III colon cancer, but did increase toxicity.

Disclosure: All authors have declared no conflicts of interest.

641P RANDOMISED PHASE III TRIAL OF CAPECITABINE + OXALIPLATIN VS. BOLUS 5-FU/LV FOR STAGE III COLON CANCER (NO16968): IMPACT OF AGE ON DISEASE-FREE SURVIVAL (DFS) OR OVERALL SURVIVAL (OS)

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Background: Adjuvant capecitabine is at least equivalent to bolus i.v. 5-FU/LV. NO16968 compared XELOX with bolus i.v. 5-FU/LV for stage III colon cancer. In a planned safety analysis, XELOX had an acceptable safety profile [Schmoll et al. 2007]. In a recent analysis of the ACCENT database, investigators concluded that the improved efficacy associated with newer adjuvant regimens vs. 5-FU/LV may not be preserved in patients (pts) ≥70y [McCleary et al. 2009].

Methods: Pts were randomized to either XELOX (capecitabine 1000mg/m^2 bid d1–14 + oxaliplatin 130mg/m^2 i.v. d1, q3w x8) or bolus i.v. 5-FU/LV: Mayo Clinic (LV 20mg/m^2 + 5-FU 425mg/m^2 d1–5, q4w x6) or Roswell Park (LV 500mg/m^2 + 5-FU 500mg/m^2 d1, w1–6 in 8w cycles x4). Treatment effects of XELOX vs. 5-FU/LV were assessed by age (≥65y, planned; ≥70y, unplanned).

Results: Of the 1886 pts randomized, 1864 were evaluable in the previously reported safety analysis. After median follow-up of 57 months, 1886 pts (ITT) were evaluated for DFS (primary endpoint), which was significantly superior for XELOX (HR=0.80; 95% CI, 0.69–0.93, p=0.0045). Analysis of 3-y DFS and 5-y OS in pts <70y and ≥70y showed a similar advantage of XELOX over 5-FU/LV.

	3-y DFS	4-y DFS	5-y DFS
Total population			
XELOX	70.9%	68.4%	66.1%
5-FU/LV	66.5%	62.3%	59.8%
	DFS by age group	OS by age group	
Overall	HR 0.80 (95% CI, 0.69–0.93)	HR 0.87 (95% CI, 0.72–1.05)	
<70y	HR 0.79 (95% CI, 0.66–0.94)	HR 0.86 (95% CI, 0.69–1.08)	
≥70y	HR 0.87 (95% CI, 0.63–1.18)	HR 0.94 (95% CI, 0.66–1.34)	

Conclusions: XELOX is superior to bolus 5-FU/LV for DFS as adjuvant treatment for stage III colon cancer; these findings confirm the benefits shown with oxaliplatin plus 5-FU combinations in stage III pts. Efficacy benefits are maintained for DFS and OS in pts ≥70y, in contrast to results from ACCENT and MOSAIC, in which no significant benefit was shown with the addition of oxaliplatin to 5-FU/LV in this age group. Reasons for this apparent difference are unknown. Current OS data indicate a trend towards superior survival with XELOX. XELOX is an effective adjuvant therapy and should be considered for all eligible patients.

Disclosure: D. Haller: Member on Advisory board: Roche, Sanofi-Aventis Corporate-sponsored research with Roche Honoraria: Roche, Sanofi-Aventis

J. Cassidy: Member on Advisory board: Roche, Sanofi-Aventis Corporate-sponsored research with Roche, Sanofi-Aventis Honoraria: Roche, Sanofi-Aventis

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E. van Cutsem: Member of Advisory board for F. Hoffmann-La Roche Corporate-sponsored research from F. Hoffmann-La Roche

F. Gilberg: Own stock: Member of Roche Connect and owing Roche Genussscheine Employed by Roche

H. Schmoll: Member on Advisory board: Roche, Merck, Merck-Sharpe and Dome Corporate-sponsored research with Roche, Merck Honoraria: Roche, Merck, Astra-Zeneca

All other authors have declared no conflicts of interest.

642P EFFICACY FINDINGS FROM THE X-ACT TRIAL OF CAPECITABINE VS. 5-FU/LV AS ADJUVANT THERAPY FOR PATIENTS WITH STAGE III COLON CANCER: NO IMPACT OF AGE ON DISEASE-FREE SURVIVAL OR OVERALL SURVIVAL

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Background: The X-ACT trial demonstrated that the oral fluoropyrimidine capecitabine is at least equivalent to bolus i.v. 5-FU/LV as adjuvant therapy for patients with stage III colon cancer [Twelves et al. NEJM 2005]. Additionally, a pre-planned multivariate analysis of the same data demonstrated the superiority of capecitabine over bolus 5-FU. In a recent analysis of the ACCENT database, investigators concluded that improved efficacy associated with newer adjuvant regimens vs. 5-FU/LV may not be preserved in patients aged ≥70 years [McCleary et al. ASCO 2009].

Methods: 1987 patients with resected stage III disease were randomised to capecitabine (n=1004) or bolus 5-FU/LV (Mayo Clinic regimen; n=983) for 24 weeks. The primary efficacy endpoint was disease-free survival (DFS). We examined DFS and overall survival (OS) retrospectively across age groups in the X-ACT trial to determine the efficacy of capecitabine in patients aged ≥70 years.

Results: After a median follow-up of 6.9 years, capecitabine was at least equivalent to 5-FU/LV in terms of DFS in the intent-to-treat (ITT) population [hazard ratio (HR) 0.88, 95% CI, 0.77–1.01; P<0.001 for upper 95% CI limit vs. predefined non-inferiority margin of 1.20]. A retrospective subgroup analysis by age shows that there is a consistent trend across all age groups for greater DFS and OS benefit with capecitabine vs. 5-FU/LV (see Table).

Age (years)	Patients (n)	5-year DFS (%)			5-year OS (%)		
		Cape	5-FU/LV	HR [95% CI]	Cape	5-FU/LV	HR [95% CI]
ITT	1987	59.1	54.6	0.88 [0.77–1.01]	70.9	67.8	0.86 [0.74–1.01]
<40	76	56.0	49.0	0.82 [0.42–1.62]	79.1	65.6	0.65 [0.30–1.44]
40–69	1513	59.4	54.5	0.87 [0.75–1.01]	70.9	68.6	0.87 [0.73–1.04]
≥70	396	58.1	55.8	0.97 [0.72–1.31]	68.8	65.0	0.91 [0.65–1.26]

Conclusions: Oral capecitabine is an effective alternative to 5-FU/LV as adjuvant therapy for stage III colon cancer and can be considered for use in all age groups, including patients aged ≥70 years.

Disclosure: C. Twelves: Member on Advisory board: Roche, Merck, Astra-Zeneca Corporate-sponsored research with Roche, Chugai, Nervian OMS Honoraria: Roche

W. Scheithauer: Member on Advisory board: Amgen, Ebewe, Roche, Merck Honoraria: Amgen, Ebewe, Roche, Merck, Sanofi-Aventis; J. McKendrick: Member on Advisory board: Roche;

J. Seitz: Member on Advisory board: Roche, Sanofi-Aventis;E. Diaz-Rubio: Member on Advisory board: Roche, Merck;F. Gilberg: Own stock: Member of Roche Connect and owing Roche Genussscheine Employed by Roche; J. Cassidy: Member on Advisory Board: Roche, Sanofi-Aventis Corporate-sponsored research with Roche, Sanofi-Aventis Honoraria: Roche, Sanofi-Aventis

All other authors have declared no conflicts of interest.

643P STROMA PRODUCTION WITHIN THE PRIMARY TUMOR CORRELATES WITH POOR SURVIVAL FOR STAGE I-II COLON CANCER PATIENTS.

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Background: The biological meaning of the stromal compartments are thought to be part of the process of wound healing, but there is also strong emphasis that CAF's (cancer-associated fibroblasts) are important promotors for tumor growth and progression. We have investigated if the amount of intra-tumor stroma can be applied as marker to identify patients for adjuvant therapy.

Methods: We have analyzed the proportion of intra-tumor stroma, on heamatoxylin-eosin (HandE) stained histological sections and distinguished between patients with

a high amount of stroma (stroma-high) and with less stroma (stroma-low). In total 135 stage I-II colon cancer patients were analyzed for this parameter and for markers involved in pathways related to stromal production and epithelial-to-mesenchymal transition (EMT). Treatment with a COX-2 inhibitor might improve patient outcome in those patients with high percentage of stroma. A series of 596 patients treated either with placebo or COX-2 inhibitor was analyzed (VICTOR-trial).

Results: Of 136 analyzed patients 35 (25.7%) were stroma-high and 101 (74.3%) stroma-low. Significant differences in survival were observed, with stroma-high patients showing poor survival (OS p<0.0001, HZ 2.59; DFS p=0.0002, HZ 2.31). A high-risk group was identified with stroma-high and SMAD4 loss (OS p=0.008, HZ 7.98, CI 4.12-15.44, DFS p=0.005, HZ 6.57, CI 3.43-12.56); 12 of 14 (85.7%) patients died within 3 years. In a logistic-regression analysis a high proportion of stroma and SMAD4 loss were strongly related (HZ 5.42, CI 2.13-13.82, p<0.001). Results of the COX-2 inhibitor are currently under evaluation but will be presented at the conference.

Conclusions: Conventional haematoxylin-eosin stained tumor slides contain more prognostic information than previously fathomed. This can be unleashed by assessing the tumor-stroma ratio. It should be considered to implement this parameter in standard pathological reports in addition to the TNM classification.

Disclosure: All authors have declared no conflicts of interest.

644P IS MUCINOUS CARCINOMA AN INDEPENDENT HISTOLOGIC TYPE IN COLON CANCER? : A SIGNIFICANCE OF MUCIN IN HISTOLOGIC CLASSIFICATION.

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The histologic classification of colon cancer (CC) has been decided on the basis of the predominant histological appearance. Cases in which mucin component occupied in more than 50% or 60% in cancer tissue are classified as mucinous carcinoma. However, there is controversy as to whether there is any difference in biological activity or prognosis from adenocarcinoma, which accounts for the majority of CC. Previous studies have made comparisons between mucinous carcinoma and non-mucinous adenocarcinoma, and there have been no studies according to the proportions of mucin. In the present study we investigated the significance of the mucin area ratio in cancer tissue as a predictor for prognosis.

Methods: The subjects were 1039 patients with CC between 1991 and 2005, and we evaluated the mucin area ratio on the maximal cut surface of the pathological specimen. Associations between age, gender, histological type, mucin area ratio, Stage, tumor site, adjuvant chemotherapy, and overall survival (OS) were assessed.

Results: Mean age was 64.5 ± 12.2 years (median age: 65 years). Histologic grade was highly differentiated adenocarcinoma in 554 cases (53%), moderately differentiated adenocarcinoma in 413 cases (40%), and poorly differentiated adenocarcinoma in 26 cases (3%), and 38 cases were mucinous carcinoma (4%). According to stage, 105 cases (10%) were Stage I, 405 (39%) were Stage II, 312 (30%) were Stage III, and 217 (21%) were Stage IV. Adjuvant chemotherapy mainly consisted of oral fluoropyrimidines was administered in 398 cases (56%). No mucin was present in 878 cases (84%). The mucin area ratio was 1—9% in 21 cases (2%), 10—29% in 49 cases (5%), 30—49% in 53 cases (5%), and >50% in 38 cases (4%). Cases with mucin > 10% accounted for 18% of those in the right colon, and were significantly more common than the 11% in the left colon. In the univariate analysis the poor OS factors in the 717 Stage II/III CC cases were poorly differentiated adenocarcinoma and absence of adjuvant chemotherapy, and neither mucinous carcinoma nor the mucin area ratio was a significant factor. In the multivariate analysis, poorly differentiated adenocarcinoma (Odds ratio: 10.1, 95%CI: 2.5-40.7) and Stage III (Odds ratio: 1.87, 95%CI: 1.4-2.5) were poor OS factors, and neither mucinous carcinoma nor the mucin area ratio was a significant factor.

Conclusions: The results of this study suggested while poorly differentiated adenocarcinoma is a poor prognostic factor in CC, mucinous carcinoma and the mucin area ratio are not significant, and that it is not necessary to manage mucinous carcinoma separately from ordinary differentiated adenocarcinoma.

Disclosure: All authors have declared no conflicts of interest.

645P CPG ISLAND METHYLATOR PHENOTYPE AND MICROSATELLITE INSTABILITY AS A PROGNOSTIC FACTOR IN COLON CANCER TREATED WITH ADJUVANT FOLFOX CHEMOTHERAPY

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Background: CpG island methylator phenotype (CIMP) is characterized by concurrent methylation of multiple CpG islands in tumor DNA, which is associated with microsatellite instability (MSI). The prognostic impact of CIMP on treatment outcome of colon cancer patients receiving adjuvant 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX) is unclear. We investigated CIMP and MSI in colon cancer patients treated with adjuvant FOLFOX.

Patients and methods: Stage II and III sporadic colon cancer patients who were treated with curative resection of primary tumor followed by adjuvant FOLFOX-4 were included. 8 CpG island loci (CACNA1G, CRABP1, IGF2, MLH1, NEUROG1, P16, RUNX3 and SOCS1) were analyzed and CIMP + was defined as 5 or more methylated loci. MSI+ was defined as 2 or more instability among the 5 Bethesda microsatellite loci. Disease-free survival (DFS) was analyzed according to molecular subtypes.

Results: A total of 144 patients were analyzed: median age 60 years (range, 30-81), male/female 86/58 patients, stage II/III 21/123, proximal/distal 51/93. 13 patients had CIMP+ and 24 patients had MSI+ tumors. CIMP+ was significantly associated with proximal location (p=0.002), mucinous histology (p = 0.036) and MSI+ (p = 0.009). DFS was negatively associated with methylation at CRABP1 (p = 0.029), IGF2 (p = 0.004), and NEUROG1 (p = 0.02). CIMP+ showed tendency towards shorter DFS (3 year DFS 69.2 % vs. 83.2%, p = 0.21). In a combined analysis of CIMP and MSI, 3 year DFS rates of CIMP-/MSI- (113 patients), CIMP-/MSI+ (18), CIMP+/MSI- (7), and CIMP+/MSI+ (6) were 83.1%, 83.3%, 85.7%, and 50%, respectively (p = 0.078). CIMP+/MSI+ showed significantly inferior DFS compared with the other patients (p = 0.01).

Conclusion: CIMP+/MSI+ subtype shows poor treatment outcome among stage II and III colon cancer patients treated with adjuvant FOLFOX. Further investigation in a larger number of patients is warranted.

Disclosure: All authors have declared no conflicts of interest.

646P CPG ISLAND METHYLATION IN MGMT, CADHERIN E AND H PROMOTERS, K-RAS AND B-RAF MUTATIONS: DETERMINING PROGRESSION AND SEQUENCE IN COLORECTAL ADENOMA-CARCINOMA

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Background: The colorectal adenoma-carcinoma sequence summarizes the epigenetic and genetic modifications which arise during cancer progression. These modifications have effect on the methylation status of different gene's promoters and mutations in the K-ras and B-raf genes. The sequence during cancer progression may be: first, methylation of H-cadherin gene promoter, followed by MGMT promoter methylation (O6-methylguanine-DNA methyltransferase) deregulating the removal of the toxic methyl adduct on guanine bases and inducing the activation of the K-ras oncogene through G to A point mutations, and finally the methylation of E-cadherin, linked to the emergence of metastasis. In order to add B-raf mutation in this sequence (showed to be linked to progression towards metastasis in CRC), we screened for mutations of B-raf genes in more than 200 colorectal cancer patients from which MGMT, E and H-cadherin methylation and K-ras status were previously determined

Method: Tumour samples were obtained from CRC patients by resection, immediately frozen in liquid nitrogen and stored at -80° until further DNA extraction by standard methods. B-raf V600E mutations were researched by TspRI digestion after PCR amplification, the mutated gene loosing the restriction site. All mutations were controlled by direct sequencing in the tumour and in its corresponding white blood cells.

Results – Conclusions: We characterized 12 mutations in the B-raf gene out of 219 tumours analysed. They were K-ras wild type confirming the fact that these mutations are mutually exclusive and tumour specific as all the sequenced blood controls were wild type. Out of these 12 B-raf mutations, 11/12 showed a MGMT and 10/12 H-cadherin promoter methylation (9 in common), but only 6/12 showed a E-cadherin promoter methylated. These results suggest that B-raf mutation arise after methylation of MGMT and H-cadherin but may arise concomitantly with the methylation of E-cadherin.

Disclosure: All authors have declared no conflicts of interest.

647P IMPORTANCE OF PERINEURAL INVASION IN EARLY STAGE COLORECTAL CANCER

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Aim: Perineural invasion (PNI) is associated w decreased survival in several malignancies. Accumulating evidence suggest PNI as a prognostic factor in colorectal cancer (CRC) but its exact significance CRC remains to be clearly defined. Herein we reviewed the data in curatively resected stage IIandIII patients (pts) to analyze the prognostic significance of PNI on disease-free survival (DFS).

Methods: Data of pts with curatively resected stage IIandIII CRC admitted to our clinic btw 2000-2007 were retrospectively analyzed. Adjuvant chemotherapy regimens were

consisted of either 5-FU or oxaliplatin based regimens. Effects of age, sex, tumor (tm) localization, tm diameter, T stage, N stage, number of total lymph nodes (LN) dissected, TNM stage, lymphatic invasion (LI), vascular invasion (VI), PNI, presence of mucine and tm grade on DFS were assessed w univariate analysis. DFS was determined using the Kaplan-Meier method, w differences determined by multivariate analysis using the Cox multiple hazards model. Results were compared using the log-rank test.

Results: A total of 209 pts (99 female) w early stage CRC were analyzed retrospectively. The median follow-up was 29.1 months (0-175). The median age was 59 (range: 19–81). The rates of T2, T3, and T4 tms were 4%, 79%, and 17% respectively. 40% of the primary tms were localized at rectum, 28% at sigmoid and 19% at right colon. LI, VI and PNI rates were 61.7%, 20%, and 33% respectively. 80% of pts received 5-FU based regimens. 3-yrs DFS for all pts was 50%. Stage III pts had significantly more PNI (25% of Stg II pts, 56% of Stg III pts, p<0,000). Univariate analyses revealed rectal localization (p=0,005), N2 disease (p<0,000), TNM stage (p=0,003), VI (p=0,003), LI (p=0,013), PNI (p=0,05) and presence of mucine (p=0,035) as prognostic factors for DFS. In multivariate Cox regression analysis; rectal disease, vascular invasion and TNM stage were independent prognostic factors for DFS.

Conclusion: On the contrary to some published reports, in the multivariate model, this study is unable to show the preanalysis hypothesis of prognostic importance of PNI on DFS in curatively resected early stage CRC pts. However it still seems to need more homogenous groups w larger number of pts to clarify this issue.

Disclosure: All authors have declared no conflicts of interest.

648P PERINEURAL INVASION IS A STRONG INDEPENDENT PROGNOSTIC FACTOR FOLLOWING PRE-OPERATIVE CHEMO/RADIOTHERAPY FOR LOCALLY ADVANCED RECTAL CANCER

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Aims: To assess the prognostic value of perineural invasion following pre-operative chemo/radiotherapy in patients with locally advanced rectal cancer.

Methodology: The study involved 94 patients with locally advanced rectal cancer treated with preoperative chemo/radiotherapy at Nottingham University Hospital between April 2001 and December 2005. Patients were treated with CT planned radiotherapy to a dose of 50Gy in 25 fractions over 5 weeks with or without concurrent capecitabine chemotherapy at a dose of 1650mg/m^2/day. Surgery was performed after an interval of 6-10 weeks. The median follow-up was 40 months (range 3-90 months).

Results: Perineural invasion was found in 19 patients (20%) in keeping with recent literature. It was found to be a strong independent prognostic factor for both disease free (p<0.0001) and overall survival (p=0.002) on Kaplan-Meier analysis. Median DFS was 12 months and OS 30 months in patients with perineural invasion. Median DFS and OS were not reached at 5 years in patients without perineural invasion. On multivariate analysis perineural invasion, nodal status, tumour regression grade and circumferential resection margin status were the most powerful predictors of both disease free and overall survival.

Conclusions: Perineural invasion is a poorly reported but very strong prognostic factor and predicts for long term outcome following preoperative chemoradiotherapy in rectal cancer. It's presence should be considered when making decisions about adjuvant treatment in rectal cancer.

Disclosure: All authors have declared no conflicts of interest.

649P EARLY DETECTION OF COLORECTAL CANCER USING MASS SPECTROMETRY BASED SERUM PROTEIN PROFILING

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Objective: Colorectal cancer (CRC) is among the most common malignancies and a leading cause of cancer-related morbidity and mortality. Early diagnosis is the most influential factor to reduce disease-related mortality. Currently only high-risk patients receive screening colonoscopy. Due to its invasive character, colonoscopy is not suitable for population-wide screening. A specific and more sensitive alternative to screening colonoscopy could be the use of proteomic biomarkers in serum.

Methods: In a randomized block design pre-operative serum samples obtained from 66 colon cancer patients and 50 controls were used to generate MALDI-TOF protein profiles using C8 magnetic beads. Next, for the analysis of a new patient series with improved magnetic beads (WCX), serum samples were obtained from 200 CRC patients and 400 healthy controls. A calibration set and a validation set were composed. MALDI-TOF protein profiles were generated after automated fractionation and spotting (96-channel pipetting robot, Hamiltonrobotics). The spectra generated using mass spectrometry (Ultraflex) were smoothed, binned and normalized after baseline correction. Linear discriminant analysis with double cross-validation, based on principal component analysis, was used to classify the protein profiles.

Results: The first study using C8 magnetic beads showed a sensitivity of 95% and a specificity of 90% in detecting CRC with an AUC of 97%. For the new series using WCX magnetic beads preliminary results show similar results. Detailed examination for different tumor stages is under evaluation. Furthermore first results are becoming available for the evaluation of serum profiles as a prognosticator.

Conclusions: The results obtained in both studies indicate potential applicability that serum protein profiles can be an option for the early detection of CRC. The automated procedure shows robust results which can be further developed for use in a population-wide screening protocol.

Disclosure: All authors have declared no conflicts of interest.

650P DEVELOPMENT AND MEASUREMENT OF GUIDELINE-BASED INDICATORS FOR COLORECTAL CARCINOMA.

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Background: Guideline adherence is not always optimal for patients with cancer. To provide information on guideline recommendations that need improvement for patients with colon and rectal cancer (CRC), this study aimed to develop and measure adherence to guideline-based indicators for CRC.

Methods: Indicators for CRC were systematically developed for diagnosis, treatment, follow-up and the organization of care using a two round RAND modified Delphi procedure. Potential guideline-based indicators were rated and then discussed in a face-to-face meeting on their usefulness to measure the quality of care. The final set was measured in a retrospective study in 22 hospitals from 3 regions in the Netherlands. Data on indicator adherence were collected by the Comprehensive Cancer Centres East, North-East and Limburg from medical records for 652 patients with CRC (diagnosed in 2006-2007). Indicators with scores < 90% were defined as having potential for improvement.

Results: Nineteen indicators were developed: seven for diagnosis, five for treatment, two for follow-up and five for the organization of care. Improvement potential was observed for 17 indicators. Lowest scores for diagnosis concerned the CT or MRI imaging of the liver (48%) and the preoperative assessment of circumferential margins with imaging techniques for rectal cancer (37%). For treatment, the lowest scores were observed for radio-chemotherapy for locally advanced rectal cancer (43%) and administration of bevacizumab in combination with chemotherapy for metastatic CRC (47%). For follow-up, a postoperative colonoscopy (in case preoperative image was incomplete) was performed in 32% of the patients with colon cancer and determination of serum carcino-embryonic antigen and performance of a CT-scan or ultrasound of liver within 6 months after surgery was performed in 15%. For the organization of care, only a minority of patients was discussed in a multidisciplinary team (32%).

Conclusion: In this study, nineteen indicators were developed for CRC of which the majority needed improvement. These results provide useful information to improve adherence to guideline recommendations and hence improve the quality of care for patients with CRC.

Disclosure: All authors have declared no conflicts of interest.

651P MGMT -535G>T POLYMORPHISM IS ASSOCIATED WITH PROGNOSIS FOR PATIENTS WITH METASTATIC COLORECTAL CANCER TREATED WITH OXALIPLATIN-BASED CHEMOTHERAPY

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The present study analyzed the polymorphisms of DNA repair genes and their impact on the response to chemotherapy and survival of patients with colorectal cancer. A total of 94 patients with recurrent or metastatic colorectal cancer treated with oxaliplatin-based combination chemotherapy were enrolled in the present study. The single nucleotide polymorphisms of 16 DNA repair genes were determined using a PCR-RFLP assay. During the median follow-up duration of 15.9 (2.1 - 53.0) months, 67 (71.3%) progression and 29 (30.9%) deaths were observed. Among the 60 patients assessable for response, response to the oxaliplatin-based regimens was found in 27 (45%) patients (9 CR and 18 PR). In a logistic regression analysis adjusted to age, sex, primary site, disease status, and regimen, the POLR2C rs4937 and MSH2 rs3732183 polymorphisms were statistically associated with the response to the oxaliplatin-based

chemotherapy. A multivariate survival analysis showed that the TT genotype of the MGMT (rs1625649) -535G>T polymorphism was found to correlate with a worse progression-free survival (PFS) than the combined GG+GT genotypes (HR = 3.137; 95% CI = 1.423–6.914; P = 0.005), which was also observed among the 60 evaluable patients (HR = 2.653; 95% CI = 1.101-6.392; P = 0.030) For the clinical parameters, curative resection was the most significant prognostic factor in a Cox model for PFS and overall survival (OS) (HR = 0.229 and 0.205; P < 0.001 and 0.001, respectively). The MGMT -535G>T polymorphism (rs1625649) was found to be correlated with PFS in patients with advanced colorectal cancer treated with oxaliplatin-based chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

652P PROGNOSTIC IMPACT OF INSULIN-LIKE GROWTH FACTOR GENE POLYMORPHISMS ON SURVIVAL OF PATIENTS WITH COLORECTAL CANCER

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Purpose: Insulin-like growth factors (IGF) regulate a wide range of biological functions including cell proliferation, differentiation, and apoptosis through paracrine and autocrine mechanisms. Accordingly, the present study analyzed polymorphisms of IGF genes and their impact on the prognosis for patients with colorectal cancer.

Methods: Four hundred and thirty-five consecutive patients with surgically resected colorectal adenocarcinoma were enrolled in the present study. The genomic DNA was extracted from fresh colorectal tissue and 8 polymorphisms of IGF genes (IGF1 -16540A>G, IGF1 +1830C>T, IGF1 -177G>C, IGF1 -533C>T, IGF1 -2995C>A, IGF2 +1280A>G, IGF2 -69C>T, IGF2 -233C>T) determined using a real-time PCR genotyping assay.

Results: The median age of the patients was 64 years (range, 21-85), and 251 (56.5%) patients had colon cancer and 193 (43.5%) patients rectal cancer. Pathologic stages after surgery were as follows: stage 0/I (n=85, 19.1%), stage II (n=149, 33.6%), stage III (n=147, 33.1%), and stage IV (n=63, 14.2%). Multivariate survival analysis including stage, age, site of disease, and CEA level showed that the progression-free survival for the patients with the IGF2 +1280 GG genotype was slightly better than for the patients with the combined IGF2 +1280 AA and AG genotype (hazard ratio [HR]=0.614, 95% Confidential Interval [CI], 0.366-1.011, P=0.056), although there was no significant difference in the overall survival. However, the other polymorphisms were not associated with survival.

Conclusions: None of the 8 IGF1 or IGF2 gene polymorphisms investigated in this study was found to be an independent prognostic marker for Korean patients with surgically resected colorectal cancer. However, further studies are warranted to clarify the role of IGF gene polymorphisms as a prognostic biomarker for colorectal cancer patients.

Disclosure: All authors have declared no conflicts of interest.

653P IS OBESITY CHANGES THE EXPRESSION PROFILE OF GENES CODING IGF IN THE COLORECTAL CANCER PATIENTS?

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Epidemiological researches indicate that obesity is the risk factor of colorectal cancer. The fatty tissue is a place of synthesis and excretion of many cytokines as IGF1, TNFα, IL-6, VEGF, TGFβ, leptin, adiponectin and others. The aim of the study was to analyse mRNA expression profile of genes coding IGF in relation to body mass index (BMI) in the colorectal cancer patients.

Material and methods: The colon cancer specimens were taken during surgery treatment of 35 colorectal cancer patients (22 men; 13 women, aged 65.5±8.9). Examined patients were divided into I-IV groups according to TNM Classification (I-7, II-9, III-10, IV-9 patients). They were divided into A and B groups as well, in relation to BMI (A:BMI<25) - 17 patients, B:BMI ≥25) - 18 patients). A number of mRNA copies of genes coding IGF1, IGF2, IGF1R and IGF2R were examined with QRT-PCR method.

Results: There were no statistical differences of mRNA copies of genes coding IGF1, IGF1R, IGF2, IGF2R in the tumor tissue between examined groups A and B. But the analysis showed that the number copies of mRNA IGF1 was enough higher in the patients with overweight and obesity than in the group with normal weight (15052±4077 versus 8558±2409). The level of mRNA genes coding IGF were similar in tissues representing different clinical staging but the analysis showed the higher number copies of IGF1, IGF1R, IGF2 according to advancement of cancer. There were no correlation between the number of mRNA copies of genes coding IGF and BMI in the group A. But there was negative correlation between the number of IGF1 and BMI (R=0.6727; p=0.330) and positive correlation between the number of IGF2R and BMI (R=0.5441; p=0.0238) in the group B.

Conclusion: The changes of expression profile of genes IGF and its receptors in colorectal cancer patients according to body mass were found. The analysis should be done among patients according to level of advancement of cancer disease, taking into consideration body mass index for the same clinical staging. The findings suggest that the changes of expression profile of genes coding IGF could be connected with autocrine and paracrine function of tumor cells in colorectal cancer. This study was supported in part by a Ministry of Scientific Research Grant NN404167234.

Disclosure: All authors have declared no conflicts of interest.

654P PHASE II STUDY WITH PANITUMUMAB, OXALIPLATIN, 5-FLUOROURACIL AND CONCURRENT RADIOTHERAPY IN HIGH-RISK LOCALLY ADVANCED RECTAL CANCER PATIENTS (STARPAN/STAR-02 STUDY)

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Background: Aim of study was to assess the activity of preoperative external radiotherapy (RT) combined with panitumumab (PAN), oxaliplatin (OXA) and 5-FU in locally advanced rectal cancer patients (pts).

Materials and methods: Pts entering the study had histologically-proven rectal adenocarcinoma, cT3N+ or cT4N-/+ stage, with location <12 cm from the anal margin. PAN was administered at a dose of 6 mg/kg IV, 2 weeks before the start of chemoradiotherapy (CTRT), and then in combination with CTRT, 3 times every 2 weeks. OXA 60 mg/m^2 IV weekly, 6 times, 1h after the PAN infusion, and 5-FU 225 mg/m^2/day CI IV days 1-38. RT was delivered at a dose of 50.4 Gy in daily fractions of 1.8 Gy. Rectal surgery was performed 7-8 weeks after the end of CTRT. Eight courses of adjuvant CT with FOLFOX4 plus PAN at the dose of 6 mg/kg, every 2 weeks, were given post-surgery. The primary endpoint was a complete pathological response (pCR) rate (ypT0N0) (Fleming's single-stage design rejected the null hypothesis ypT0N0 </= 24%).

Results: Sixty eligible pts were enrolled from February 2007 to October 2009. Pt characteristics: M 40 (66.7%), F 20 (33.3%); median age 60 (37-75); clinical stage: T3 66.1%, T4 25.0%, Tx 8.9%, N- 20.0%, N+ 72.7%, Nx 7.3%. Five pts did not undergo surgery: 2 disease progression, 1 toxic death (diarrhea), 2 refusal. Fifty-five (91.7%) pts underwent surgery and were evaluable for pathological response. pCR (ypT0N0) was 21.1% (95% CI, 10.4 to 31.6%) in 12/57 pts (55 resected + 2 progression disease pts). Pathological downstaging occurred in 33/57 pts (57.9%). Grade 3-4 toxicity: diarrhea 40.0%, rash 23.7%, nausea 5.1%, asthenia 3.4%, anorexia 3.4%, neutropenia 1.7%, vomiting 1.7%.

Conclusions: The primary end-point is not reached in the Starpan Study. However, in this study the addition of PAN to 5-FU/OXA CTRT showed an higher pathological complete response rate in comparison to the results of other previous neoadjuvant rectal cancer clinical trials based on anti-EGFR monoclonal antibodies. This PAN combination treatment is associated with high incidence of grade 3-4 diarrhea.

Disclosure: All authors have declared no conflicts of interest.

655P CRAB TRIAL: UPDATED RESULTS FROM A PROSPECTIVE PHASE II STUDY EVALUATING NEOADJUVANT CAPECITABINE, RADIOTHERAPY (RT) AND BEVACIZUMAB IN LOCALLY ADVANCED RECTAL CANCER

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Objectives: Preoperative capecitabine-based chemoradiation (CRT) is a standard treatment for locally advanced rectal cancer. Combining bevacizumab with CRT may increase antitumor efficacy by maximizing inhibition of the VEGF pathway. Thus, we sought to explore the safety and efficacy of the addition of bevacizumab to capecitabine and concurrent RT for locally advanced rectal cancer.

Methods: Enrolled patients (pts) with MRI-confirmed stage II/III rectal cancer were treated with an infusion of Bev (5 mg/kg) 2 weeks prior to neoadjuvant CRT, followed by Bev 5mg/m^2 on week 3, 5, 7 and capecitabine 825 mg/m^2 bid including weekends during RT. RT was administered at 50.4 Gy (25×1.8 Gy with boost 3×1.8 Gy, 3D conformal technique), starting on week 3. Total mesorectal excision was scheduled 6-8

weeks after completion of CRT. Tumor regression grades (TRG) were evaluated on surgical specimens according to Dworak. The primary endpoint was complete pathologic response (pCR).

Results: Fourty-two of 61 pts enrolled were eligible for safety and efficacy analyses. Median age was 60 (range: 31–79) years, 64% of pts were male. Seven pts (16.6%) had T3N0 tumors, 11 pt (26.1%) T3N1, 2 pt (4.7%) T2N2, 18 pts (42.9%) T3N2, and 4 pts (9.5%) T4N2. In 22 pts (52.4%) tumor invaded the mesorectal fascia. The median tumor distance from anal verge was 6 (range: 0–11) cm. All pts received 50.4 Gy RT and 4 Bev infusions. Temporary capecitabine intake interruption was necessary for 2 pts (4.8%) due to leucopenia grade 2, for 1 pt (2.4%) due to leucopenia grade 3 and for 1 pt (2.4%) due to diarrhea grade 3. Other grade 3 toxicities included dermatitis (n=6, 14.3%) and proteinuria (n=3, 7.1%). Radical resection was achieved in 39 pts (92.9%) and 31 pts (73.8%) had sphincter preserving surgery. TRG 4 (pCR) was recorded in 5 pts (11.9%) and TRG 3 in 6 pts (14.3%). T-, N- and overall downstaging rates were 45.2%, 73.8% and 73.8%, respectively.

Conclusions: This updated analysis shows the feasibility of preoperative CRT with bevacizumab and capecitabine. The observed adverse effects of neoadjuvant treatment in our study are comparable to those previously reported, but the pCR rate appeared to be much lower.

Disclosure: All authors have declared no conflicts of interest.

656P CHEMORADIOTHERAPY WITH 5-FU VERSUS CAPECITABINE ON RECTAL CANCER DOWNSTAGING

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Background: The treatment of locally advanced rectal cancer with preoperative radiotherapy and concurrent 5-fluorouracil (5-FU)-based chemotherapy on improves local tumor control, increasing resectability and rate of sphincter preservation.

Aim: Comparing the results of preoperative chemoradiotherapy with continuous infusion of 5-FU versus capecitabine (C) in the treatment of locally advanced rectal cancer in our institution.

Material and methods: Retrospective analysis of clinical records of patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy between January'2003 and January'2010 in our institution. Chi-square test was used to establish the relation between variables.

Results: There were 133 patients (39,8% female and 60,2% male), with a median age of 63-year-old at diagnosis. The primary tumor location was in lower rectum in 52,6% of patients, in medium rectum in 38,3% and in high rectum in 9,0%. The majority (62,4%) of patients presented with IIIB clinical stage at diagnosis (stage IIA – 29,3%; IIB – 5,3%; IIIC – 0,8%; IVA – 2,3%). 5-FU was administered at a dose of 225mg/m2/day in continuous infusion during radiotherapy in 59,4% of patients, and C was given at a dose of 825mg/m2 twice a day in 33,1%. Patients received a total radiation dose between 46 and 50Gy, in 23 to 25 fractions, with 18Mv energy. All patients underwent definitive surgery 6-8 weeks after chemoradiotherapy completion. Low anterior resection was made in 50,4% of patients and abdominoperineal ressection in 39,8%. In 37,1% of patients with lower rectum tumors, sphincter preservation was made possible. Downstaging was achieved in 60,9% of cases and a pathological complete response (pCR) in 13,5%. There was no identified statistical significant difference between the use of 5-FU or C on downstaging (p=0,749), pCR (p=0,556) and type of surgery (p=0,831).

Conclusion: The use of 5-FU or C, in addition to radiotherapy in preoperative treatment of locally advanced rectal cancer, allows downstaging and pCR, with possibility of sphincter preservation. There was no difference between the use of this two drugs in downstaging and pCR in our institution practice, which is in agreement with the international literature.

Disclosure: All authors have declared no conflicts of interest.

657P FINAL SAFETY AND EFFICACY RESULTS OF A PHASE II TRIAL OF BEVACIZUMAB, CAPECITABINE, OXALIPLATIN, RADIATION RECTAL CANCER TRIAL (A-CORRECT)

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Background: The objectives of this trial were to evaluate the safety and efficacy of pre-operative (Pre-op) chemoradiation with capecitabine (Cap), oxaliplatin (Ox) and bevacizumab (Bev) with standard doses of radiation in patients (pts) with high risk rectal cancer.

Methods: Pts with locally advanced or low rectal cancer were treated with Cap 825 mg/m^2 days (d) 1-14 and 22-35, Ox 50 mg/m^2 d 1,8,22 and 28 and Bev 5mg/kg d(-)14, 1, 15 and 29 and radiation, 50.4 Gy/28d, including boost. Surgery was performed 7-9 weeks after completion of radiation. The primary endpoint was to achieve a pathologic Complete Response (pCR) of ≥ 25% by central review. A total of 37 evaluable patients would be required to test the hypothesis with an alpha=0.1 and beta=0.2.

Results: 43 pts were enrolled at 6 centers of which ≥42 were evaluable for toxicity and 37 for response. Median age was 61 and 9 (21%) patients had T4 tumors. Four of 42 patients received <50.4Gy due to adverse events (AEs). Most common Grade (Gr) 3/4 pre-op toxicities were diarrhoea 10(24%), pain 4(9.5%) and fatigue 4(9.5%). Of 38 patients who had surgery 5(13%) had Gr 3/4 pain, fatigue or infection. Pre-specified AEs are presented in Table I. pCR was seen in 7(19%) and central review changed pathologic stage in 6(16%) of cases.

Event, n (%)	Pre-operative		Post-operative	
	All	Gr3/4	All	Gr3/4
Bleeding	7 (17)	0	4 (11)	1 (3)
Fistulae	0	0	3 (8)	0
Infection/Abscess	5 (12)	2 (5)	13 (34)	7 (13)
Delayed Wound Healing	-	-	7 (18)	3 (8)
Anastomotic Leak	-	-	6 (16)	2 (5)
Viscus Perforation	0	0	0	0

Conclusions: In this study, Bev added to Ox and Cap in combination with radiation was safe but did not significantly increase pCR. Further study of pre-operative Bev with other regimen or induction chemotherapy may be warranted. Central pathology review should be considered for trials with pCR as the primary endpoint.

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658P CRITICAL ROLE OF BEVACIZUMAB SCHEDULE IN COMBINATION WITH CHEMO-RADIOTHERAPY IN NEO-ADJUVANT TREATMENT OF RECTAL CANCER: CIRCULATING ENDOTHELIAL CELLS AND FDG-PET AS MARKERS FOR EARLY PREDICTION

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In this study in order to demonstrate the relevance of the timing of bevacizumab (BEV) added to primary chemotherapy (CT) and radiotherapy (RT) we evaluate two different schedules of BEV in pts with locally advanced rectal cancer. Changes of circulating endothelial cells (CECs) and glucose metabolism, evaluated by flow cytometry and FDG-PET respectively, were used as early surrogate markers of tumor response. Thirty-two patients (inclusion criteria: cT4, cN+, cT3≤ 5 cm from the anal verge and/or +ve CRM, M1 resectable/initially unresectable) received 3 biweekly courses of oxaliplatin (100 mg/m2)/ raltitrexed (2.5 mg/m2) on day 1, and fluorouracil (800 mg/m2)/ folinic acid (250 mg/m2) on day 2 during pelvic RT (45 Gy). In schedule A (16 pts) BEV (5 mg/kg) was given biweekly from day -14 for 4 courses, while in schedule B (16 pts) it was given from day -4 for 2 courses. According to the Simon's two-stage design, assuming an hypothesis of a 50% TRG1 (α error=0.05, β error=0.20), at least 6/16 TRG1 should be obtained (first stage) to continue pts accrual. Grade $^3/_4$ neutropenia was the most common adverse event with the schedule A (7 pts, 44%), but it was considerably lower with the schedule B (2 pts, 13%). Notably, a significant difference of CEC levels, compared to basal levels, was observed, 2 days after first cycle of CT, between the two schedules of treatment (median +6% and -84% in schedule A and B, respectively, p<0.05). Likewise, a major reduction of median tumor metabolic volume was observed, 12 days after first cycle of CT, in schedule B compared to schedule A (-75% vs -50%, p<0.05). Furthermore, while in the schedule A only 2 (12%) pts obtained a TRG 1, in the schedule B the number of TRG 1 required by statistical design was reached in the first 16 treated pts (9 ; 56%). Therefore, accrual in the schedule B will continue to complete the second stage. Overall these data suggest the relevance of the BEV schedule to optimize the feasibility and efficacy of combination treatment, as well as the potential role of CEC evaluation and

FDG-PET for the early prediction of response to anti-angiogenesis therapeutical approaches.

Disclosure: All authors have declared no conflicts of interest.

659P THE LOCATION OF LYMPHANGIOGENESIS IS AN INDEPENDENT PROGNOSTIC FACTOR IN RECTAL CANCERS WITH OR WITHOUT PREOPERATIVE RADIOTHERAPY

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Background: Lymphangiogenesis and angiogenesis are essential for tumor development and progression. The lymphatic vessel density (LVD) and blood vessel density (BVD) and their relationship to outcome have been studied extensively, however the clinical significance of the location of LVD/BVD in tumor is not known. In the present study, the location and degree of LVD/BVD and their relationship to preoperative radiotherapy (RT), clinicopathologic, histopathologic and biologic factors were studied in rectal cancer patients participating in a Swedish clinical trial of preoperative RT.

Patients and methods: The location and degree of LVD/BVD were analysed in primary tumors (n=138/140) and their subgroups of non-RT (n=74) and RT (n=64/66). Further the degree of LVD/BVD was examined in the corresponding distant normal mucosa (n=35/31) and adjacent normal mucosa (n=72/91). All sections were immunohistochemically examined by using D2-40 and CD34 antibodies.

Results: In the whole series of the patients, a higher LVD at the periphery was related to negative p53 expression (P=0.03) and favourable survival independent of TNM stage, differentiation and p53 expression (P=0.03). LVD was increased in p53 negative tumors after RT (P=0.01).

Conclusions: LVD at the periphery of the tumour was an independent prognostic factor in rectal cancer patients.

Disclosure: The author has declared no conflicts of interest.

660P BIOMARKER PROFILES ARE NOT OF PREDICTIVE VALUE FOR RESPONSE AND OUTCOME IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER UNDERGOING CETUXIMAB-BASED PREOPERATIVE CHEMORADIOTHERAPY

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Background: Results of our phase II trial in pts with LARC treated with standard radiation plus capecitabine, oxaliplatin and cetuximab have shown that this regimen is feasible without a significant improvement of pathohistological response (Rödel et al., 2008). Although a certain subgroup of pts might benefit, there is no effective method to predict treatment efficacy. To identify potential biomarkers, we analyzed EGFR, PTEN, Ki67, survivin and p53 in order to investigate their predictive value in LARC pts treated with the cetuximab-based therapy.

Methods: Pre- and posttherapeutic specimens from 47 pts of the phase II trial were taken before treatment as biopsies and at the time of surgery. Correlation of expression pattern of the biomarkers was done with pathohistologic response (modified classification by Dworak et al., 1997), PFS and OS.

Results: EGFR expression was significantly lower ($p<0.001$) after treatment, with the proportion of pts with EGFR null-expression increasing from pretreatment 52% to posttreatment 91% (p=0.0002). Initial EGFR expression did neither significantly correlate with response (p=0.12) nor with PFS or OS (p=0.59 and p=0.63). In contrast to EGFR, PTEN expression increased after treatment (p=0.004). Initial PTEN expression did not significantly correlate with response (p=0.36) and PTEN upregulation was neither associated with PFS nor with OS (p=0.99 and p=0.55). Posttreatment Ki67 expression was significantly lower (p=0.001) without a significant correlation between initial expression of Ki67 and response (p=0.56), PFS (p=0.11) or OS (p=0.31). We did not observe a significant association between pre- and posttreatment expression of survivin (p=0.09) and p53 (p=0.52) and regression grade. High initial expression of p53 was not found to be predictive for PFS (p=0.48) or OS (p=0.38) and survivin not significantly associated with PFS (p=0.58) or OS (p=0.68).

Conclusions: Cetuximab-based chemoradiotherapy resulted in downregulation of EGFR and Ki67 expression and in upregulation of PTEN. However, expression of EGFR, PTEN, Ki67, survivin and p53 did not predict tumor regression grading, PFS or OS.

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661P CIRCULATING LEVEL OF VEGF, E-SELECTIN, TGF-α, EGF AND 18F-FDG PET UPTAKE IN LOCALLY ADVANCED RECTAL CANCER (LARC) PATIENTS TREATED WITH CHEMORADIATION (CTRT) AND PANITUMUMAB (STARPAN/STAR-02 PHASE II STUDY)

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Background: The aim of this study was to explore changes in circulating VEGF, sE-Selectin, TGF-α, EGF and 18F-FDG PET uptake produced by panitumumab-based CTRT in LARC pts.

Methods: Pts entering the study had rectal adenocarcinoma, cT3N+ cT4N-/+, with location <12 cm from anal margin. Panitumumab was administered at a dose of 6 mg/kg IV, 2 weeks before the start of CTRT and then 3 times every 2 weeks. CT consisted of 5FU 225 mg/m2/day CI IV days 1-38 and OXA 60 mg/m2 IV weekly six times. RT was delivered at a dose of 50.4 Gy. Rectal surgery was performed 7-8 weeks after the end of CTRT. Serum/plasma VEGF, sE-Selectin, TGF-α, EGF levels were determined on day -14 (baseline) and on days 1 (after panitumumab), 8 and 22 (during treatment), and 36 (pre-surgery). Biomarkers levels were assessed using commercial quantitative sandwich enzyme immunoassays (Quantikine Human VEGF Immunoassay, RandD Systems; Human sE-selectin ELISA, Bender MedSystems; Quantikine Human EGF Immunoassay, RandD Systems; Human TGF-α TGF RayBio). 18F-FDG-PET scan was performed at baseline and after first panitumumab infusion (days -14, 1).

Results: From February 2007 to October 2009 23, out of 62 StarPan study pts, were available for biomarker evaluation and 28 for PET study. The median biomarker basal values (day -14) were: sVEGF 465.7 pg/ml, pVEGF 114.2 pg/ml, E-Selectin 35.0 ng/ml, TGF-α 33.4 pg/ml, EGF 534.4 pg/ml. On day 1, after only one panitumumab infusion sVEGF, E-Selectin and TGF-α median levels were higher: sVEGF 555.0 pg/ml (p 0.027), E-Selectin 50.5 ng/ml (p <0.001) and TGF-α 68.1 pg/ml (p 0.006). Median SUV decreased from 16.1 (range 6.1-26.9) at baseline to 10.2 (range 1.9-25.2) after panitumumab administration (p 0.019). The EGF level after panitumumab administration was 418.3 pg/ml and significant decrease at day 36 (pre-surgery time) 339.0 pg/ml (p 0.001).

Conclusions: A single dose of panitumumab has a significant impact on upregulation of sVEGF, E-Selectin and TGF-α and decreased the 18F-FDG uptake. The EGF level showed a decreasing trend from panitumumab administration that reached significance in the pre-surgical phase.

Disclosure: All authors have declared no conflicts of interest.

662P TOPOISOMERASE IIα IN COLORECTAL CARCINOMA: EXPRESSION AND PROGNOSTIC ROLE

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Aim and background: Since very few data have been published, the aim of this study was to investigate the expression and prognostic role of topoisomerase IIα in patients with colorectal cancer (CRC).

Patients and methods: The expression of topo IIα was evaluated immunohistochemically (IHC) on archival paraffin-embedded samples of CRC tissue from 146 patients, 59 (40.4%) females and 87 (59.6%) males, operated on in our hospital at Department of Surgery. Their median age was 65 years (range 35-87). There were 32 (22.1%) Dukes A, 46 (31.7%) Dukes B, 46 (31.7%) Dukes C tumors and 21(14.5%) tumors with distant metastasis. IHC was carried out by using the MoAb anti-human TOPO-IIa antibody (DAKO No K 0355). Immunoreactivity was scored semiquantitatively so that patients could be divided into the three groups according to the percentage of tumor cells staining topo IIα positive: group 1 (≤ 10%; n = 10 (7%)), group 2 (11-50%; n = 85 (58%)) and group 3 (>50%; n = 51 (35%)). Obtained IHC results were correlated with the following clinicopathological parameters: tumor stage (Dukes classification), tumor grade, vascular invasion and patients survival. All results are expressed as median (range).

Results: The follow up period was 72 (0-95) months. A trend toward statistically significant worse survival was observed for the patient group 1 (30%) comparing to group 2 (57.6%) and group 3 (51.0%), but result was not statistically significant (30% vs 57.6%, p = 0.051; 30% vs 51%, p = 0.131). Toppo IIα expression was not found to be statistically different among patients arranged according to the Dukes tumor stage (Dukes A = 35%; B = 35%; C = 32.5%; tumor stage with distant metastases = 40%). Also, there was no significant correlation between the topo IIα expression and tumor grade (g) (g 1 = 40%, g 2 = 35%, g 3 = 35%), vascular invasion (without = 35%, with = 40%) and lymph node affection (N0 = 35%, N+ = 40%).

Conclusion: No significant correlation between the mentioned clinicopathologic parameters and the topo IIα was identified. The only exception were the patients' survival data which showed worse survival in patients with lower expression of topo IIα, but without statistical significance. Due to relative rarity of this type of research, additional studied in larger cohort of patient are needed.

Disclosure: All authors have declared no conflicts of interest.

663P A LET-7 MICRORNA COMPLEMENTARY SITE POLYMORPHISM IN THE KRAS 3'-UTR REGION AS A GENETIC REGULATOR IN ADVANCED COLORECTAL CANCER

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Background: Although KRAS status has been identified as a strong predictor of resistance to anti-EGFR therapies, not all wild type patients respond. Let-7 family of microRNAs regulates KRAS expression and has been associated with colorectal cancer outcome. The fact that the functional KRAS-LCS6 variant affects the KRAS expression led us to hypothesize a possible association between the KRAS-LCS6 polymorphism and the response to anti-EGFR treatments.

Patients and methods: In this study were included 91 patients with KRAS wild type metastatic colorectal adenocarcinoma treated with anti-EGFR antibodies in monotherapy or in combination with chemotherapy. We genotyped all patient samples for the KRAS-LCS6 polymorphism using the 48.48 dynamic array chips on the BioMark™ system (Fluidigm)

Results: Seventy seven patients presented LCS6 T/T genotype (85%) while 14 were T/G and G/G (15%). Two patients (2%) had CR, 20 had PR (22%), 36 had SD (40%) and 26 progressed (29%). LCS6 G-allele showed statistically significant association with non-response; 31% of patients with T/T genotype presented CP or PR vs no patients with T/G or G/G genotypes (p=0.031). Multivariate analysis confirmed that KRAS-LCS6 polymorphism and skin toxicity were independently related with response (p<0.05).

Conclusions: Presence of the LCS6 G-allele can predict clinical response to anti-EGFR treatment in patients with KRAS wild type metastatic colorectal adenocarcinoma.

Disclosure: All authors have declared no conflicts of interest.

664P CIRCULATING TUMOR CELLS IN COLORECTAL CANCER. A PROSPECTIVE STUDY

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Introduction: Detection of circulating tumor cells (CTCs) from the peripheral blood has been proposed as prognostic and predictive factor in breast, prostate and colon cancer. Confirmation of this hypothesis would be relevant for the correct selection of treatments.

Methods: We have performed a prospective cohort study in patients (pts) with metastatic colorectal cancer. Quantification of CTCs in 7.5 ml of blood was carried out with the CellSearch® System. Serial blood samples were collected at the start of chemotherapy, before the 2nd cycle and the 3rd and 6th months (m); case of rescue surgery the sample would be taken before and after the surgery. The results were expressed as number of CTCs/7.5 ml; >= 3 CTCs/7.5 ml was defined as positive test. The aim of this study was to correlate the presence of CTCs with the progression free survival (PFS)

Results: From Feb to Dec 2009 CTCs were enumerated in 60 pts before the initiation of treatment: 36 men/24 women, median age was 64 years (36-81), 36% rectal cancer/64% colon cancer, 32 pts (53%) had only liver metastases and 41 pts (68%) were operated from primary tumor. Rescue liver surgery was performed in 22 pts. The median follow up was 6 m. Positive CTCs were detected in 26 of 60 pts (43%); median 2 CTCs (range 0-58). Before the second cycle of chemotherapy in 12 of 24 pts CTCs were positive (median 2 CTC; 0-54), at 3 m in 5 of 30 pts (median 0; 0-15) and at 6 m in 6 of 20 pts (median 0.5; 0-40). Pts who received liver surgery had a median of 0.5 CTC (0-7) before surgery and 1 CTC (0-9) after surgery. Mean CTCs in pts with palliative chemotherapy was larger than in pts candidates to surgery: 8.5 vs 1.7 (p = 0.021). PFS was 8 m from the entire cohort. Pts with <3 CTCs had PFS 10 m (IC95: 6.6-13.4) and pts with >= 3 CTCs had PFS 5 m (IC95: 2.7-7.3); p = 0.059. Evaluations before the 2nd of chemotherapy (24 pts), at 3 m (30 pts) and at 6 m (20 pts) show different prognosis in pts with <3 CTCs versus. >= 3 CTCs but it theses differences aren't still significant probably because the low number of pts and the short follow-up.

Conclusion: This study suggests that measurement of CTCs in colorectal cancer pts is a useful prognosis tool for PFS. The relationship with response and overall survival must be determined in this series with a larger follow-up.

Disclosure: All authors have declared no conflicts of interest.

665 IS ADVENCED PARENTAL AGE A RISK FACTOR FOR COLORECTAL CANCER? TURKISH ONCOLOGY GROUP STUDY

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Backround: There is some evidence that prenatal factors can play role in development of colorectal cancer. This trial is designed to investigate the effects of some prenatal factors on colorectal cancer risk.

Materials and methods: In the present study 261 in or out patient diagnosed as colorectal cancer and 522 control patients included. Groups were asked the parental age, smoking habits, sociodemographic, environmental, familial and reproductive traits. The results were compared between the parents and the control group.

Results: In this study, it was determined that children may have higher risk if mother and father are more than 30, at birth (p= 0.002 and p= 0.002, respectively). While the mean mother age at birth was 27,7 ± 6,5 in patients, it was 26,4 ± 7,3 in the controls. The difference was statistically significant (p= 0.002). While the mean father age at birth was 31,1 ± 7,3 in patients, it was 29,8 ± 8,4 in the controls. The difference was statistically significant too (p= 0.003). It was detected that cancers other than colorectal is more frequent in first degree relatives of colorectal cancer patients (p< 0.001). People smoking or quitted smoking have more risk for colorectal cancer (p= 0.013). In this study indicate that a lower risk of colorectal cancer is associated with higher levels of coffee consumption (p= 0.006). Increased animal oil, and alcohol consumption is found to be associated with colorectal cancer (p= 0.003, and p< 0.005 respectively). It was detected that milk-dairy product, and vegatable-fruit consumption are more frequent in patients than the controls (p< 0.001, and p< 0.001). In this study, when colorectal cancer patients are compared to control group, menarche age, paternal smoking, kinship between mother and father, family type, total meat consumption, drinking tea habit, daily physical activity, socioeconomical situation, and educational level aren't found to be a risk factor for colorectal cancer.

Conclusion: Our data supports that some prenatal factors such as high parental age at birth may be risk factors for colorectal cancers. So, more comprehensive studies are needed about the effects of prenatal factors.

Disclosure: All authors have declared no conflicts of interest.

666 PROGNOSTIC VALUE OF SERUM CARCINOEMBRYONIC ANTIGEN (CEA) IN FIRST LINE TREATMENT OF ADVANCED COLORECTAL CANCER (ACRC)

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Background: The clinical value of CEA as the marker for monitoring the response of advanced colorectal cancer (ACRC) to systemic therapy is not clearly established. The aim of this study was to prospectively evaluate the usefulness of CEA.

Patients and methods: Previously untreated histopatologically confirmed ACRC, age > 18 years and Karnofsky (PSK) [3] 60% were treated with capecitabine (850 mg/m2 twice a day p.o. on days 1-14), irinotecan (240mg/m2 on day 1) and bevacizumab (7.5 mg/Kg on day 1), in a 3-week cycle. Response was evaluated every 2-3 month, CEA was checked on day 1 of every cycle. Response by CEA was defined as a reduction of 50%, and progression as an increase of 30%.

Results: From March 2005 to July 2009, 148 patients (pts) entered in the study. 111 pts have progressed to first line treatment and 71 have died. CEA was 2x upper normal limit (UNL) in 106 (71,6%), 5x UNL in 84 (56,7%), inferior a 2x ULN in 13 (8,7%), and

normal (<5 ng/mL) in 29 (19,5%) pts. 15 pts with normal baseline CEA have progressed, and CEA increased in 8 (53%) during first or successive lines. For response, there were 65 pts truly positive (TP), 21 truly negative (TN), 24 false positive (FP), and 2 false negative (FN). So resulted in sensitivity (S) of 97% (CI 95%, 88.68-99.48%), specificity (Sp) of 46.67% (CI 95%, 31.93-61.96%), positive predictive value (PPV) of 73.03%, and negative predictive value (NPV) of 91.3%. An accuracy of 76.79%. For progression, there were 98 TP, 7 TN, 22 FN, and no FP. So resulted in S of 81,6% (CI 95%, 73.3-87.9%), Sp of 100% (CI 95%, 56.1-100%), PPV of 100%, and NPV of 24.1%. An accuracy of 75.6%. CEA indicated progression and response with a median of 46 and 43 days prior to the computed tomography (CT) scan, respectively. OS and TTP was statistically higher for patients with basal CEA< 2 x Upper Normal limit (UNL) and < 5 X UNL. TTP to first line treatment was higher if a response in CEA was detected (p< 0.001). In patients with no radiologic response but CEA response, a trend in TTP was detected (p=0.069).

Conclusions: CEA is simple and accessible test that can predict the radiologic behavior; and is a prognostic factor for OS and TTP. These results suggest that CEA could help in the decision of accelerate or delay CT scan in order to avoid un-useful treatments/CT scan.

Disclosure: All authors have declared no conflicts of interest.

667 IS A PATHOLOGICAL COMPLETE RESPONSE A SURROGATE MARKER OF RECURRENCE-FREE SURVIVAL AFTER PREOPERATIVE CHEMORADIOTHERAPY FOR LOCAL ADVANCED RECTAL CANCER?

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Background: The clear-cut evidence that an increased pCR rate leads to better long-term outcomes is lacking. Nonetheless, retrospective studies suggesting a relation between pCR and improved long-term outcomes have been reported sporadically.

Objectives: We conducted phase I/II studies of chemoradiotherapy with S-1and irinotecan in patients with locally advanced rectal cancer treated in our hospital to evaluate pathological results and outcomes and to clarify the clinical significance of pCR as a short-term endpoint.

Subjects: The study group comprised 76 patients with locally advanced rectal cancer (T3 or T4, any N) who were enrolled in phase I/II studies of preoperative chemoradiotherapy with S-1 and irinotecan, given in the recommended (irinotecan, 80 mg/m^2; S-1, 80 mg/m^2) or lower doses.

Results: The median follow-up period was 4 years, and 15 patients (19.7%) had recurrence. Recurrence rates according to the pathological response at the time of surgery were as follows: 30.4% (14/46) for non-pCR , and 3.3% (1/30) for pCR. Immunostaining of biopsy specimens obtained before treatment showed significant overexpression of Ki-67 labeling index, Bax, and thymidylate synthase in patients who responded to treatment.

Conclusions: Chemoradiotherapy with S-1 and irinotecan is a new regimen with a very high rate of pCR. The recurrence rate was low among patients who responded to chemoradiotherapy, and many patients with recurrence had advanced-stage lymph-node metastasis or lateral node-positive disease. Patients with a milder response to treatment had a high rate of recurrence, apparently unrelated to the presence or absence of lymph-node metastasis. The rate of recurrence was extremely low in patients who responded to preoperative therapy, particularly in those with pCR. These results suggested that pCR may be a surrogate marker of recurrence-free survival in patients with locally advanced rectal cancer. Immunostaining of biopsy specimens obtained before treatment may enable the identification of patients most likely to respond to therapy, thereby facilitating the design of individually tailored regimens.

Disclosure: All authors have declared no conflicts of interest.

668 A PHASE II MULTICENTER TRIAL OF NEOADJUVANT CHEMOTHERAPY WITH BEVACIZUMAB PLUS MFOLFOX6 FOR RESECTABLE CASES OF SYNCHRONOUS LIVER METASTASIS FROM COLORECTAL CANCER: THE FIRST INTERIM ANALYSIS

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Background: Treatment for synchronous liver metastases from colorectal cancer (CRC) has not been defined. A phase II multicenter trial of neoadjuvant chemotherapy for resectable cases of synchronous liver metastasis was started on June 2008 (Miyagi HBPCOG-004).

Purpose: This interium analysis was to evaluate the efficacy and the toxicity in 20 patients.

Patients and methods: Patients were enrolled after R0-resection of original CRC, and received in total 8 courses of chemotherapy. In the 2nd to 7th courses, patients received chemotherapy with bevacizumab (5 mg/kg), oxaliplatin (85 mg/m2), leucovorin (200 mg/m2) and 5-Fluorouracil (400 mg/m2 as i.v. bolus and 2400 mg/m2 as continuous infusion of 46h) every two weeks. In the 1st and 8th courses, bevacizumab was omitted from this regimen to avoid adverse events. The primary endpoint was the response rate (RR).

Result: One case was diagnosed as benign tumor after enrolment. Therefore, 19 patients were analyzed for the response. Complete and partial responses were achieved in 2 (10.5%) and 9 (47.4%) patients, respectively (RR: 57.9%); 2 (10.5%) patients had stable disease and one (11.3%) progressive disease. One case was dropped for grade 3 stomatitis before assessment, and in 4 cases there was not enough time to confirm the RECIST such as by operation. The best responses in these 4 cases were below, 3 cases were partial response (15.8%) and one case was stable disease (11.3%). Including these four cases, complete and partial response was achieved in 2 (10.5%) and 12 (63.2%) patients, respectively (RR: 73.7%). Grade 3 adverse event (AE) of neutropenia occurred in 4 cases (20.0%), and sensory neuropathy, stomatitis, diarrhea, and cerebral infarctions occurred in one case (5.0%). Liver resections were performed in 17 out of 20 cases, and and R0 resection was done in all operative cases.

Conclusion: Chemotherapy with bevacizumab plus mFOLFOX6 for liver metastases appears to be effective and well tolerated. This strategy for the initial treatment of synchronous liver metastases merits further evaluation. TRIAL REGISTRATION: UMIN Clinical Trials Registry (UMIN-CTR) UMIN000000996

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669 PREOPERATIVE TREATMENT FOR COLORECTAL LIVER METASTASES: IMPACT ON HEPATIC HISTOLOGY AND POSTOPERATIVE OUTCOME

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Background: preoperative chemotherapy before resection of hepatic colorectal metastases (CRM) may cause hepatic pathological change and clinical outcome. The objective of this study was to assess the effects of preoperative treatment on the hepatic histology of non-tumorous liver and postoperative outcome.

Patients and methods: 106 patients underwent hepatic resection for CRM between 1999 and 2009. The surgical specimens were reviewed using established criteria for diagnosis and grading of pathological liver changes. The effect of preoperative treatment and liver injury on postoperative outcome was analyzed.

Results: 53 patients (50%) received no preoperative chemotherapy, whereas 42 patients (39.6%) received neoadjuvant chemotherapy, and 11 (10.4%) patients received preoperative transcatheter arterial chemotherapy (TACE). The median duration of chemotherapy was 5 cycles (range, 2-10 cycles). Chemotherapy consisted of oxaliplatin-based regimen (31.1%) and irinotecan-based regimen (8.5%). On pathologic analysis, 16 patients (15.1%) had steatosis, 31 (29.2%) had sinusoidal dilation and 20 patients (18.9%) had steatohepatitis. Oxaliplatin was associated with sinusoidal dilation compared with no preoperative treatment (42.4 % v 20.8%, P=0.03; OR=2.81; 95% CI, 0.97 to 8.2), and sinusoidal dilation increased postoperative complication rate compared with no sinusoidal dilation (P=0.009). Preoperative chemotherapy was associated with pathologic hepatic injuries compared with no preoperative treatment (57.1% vs. 35.8%, P=0.04), and increased liver injuries in patients who received 6 or more cycles of chemotherapy when compared with patients with less than 6 cycles (P=0.01). TACE have a higher likelihood of steatosis and steatohepatitis compared with no preoperative treatment.

Conclusions: Preoperative oxaliplatin was associated with sinusoidal dilation. In patients with hepatic CRM, the preoperative chemotherapy can increase the pathologic hepatic injuries, and longer-duration chemotherapy appear to be associated with increased liver injuries. TACE can cause the histopathologic changes by affecting the non-tumorous hepatic parenchyma.

Disclosure: All authors have declared no conflicts of interest.

670 THE ROLE OF CONTRAST-ENHANCED ULTRASOUND IN DETECTION OF LIVER METASTASES FROM COLORECTAL CANCER: 2 YEARS UPDATE RESULTS

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Background: Up to 15-25% of patients with colorectal cancer (CRC) will develop metacronous liver metastases during the follow-up. The management and prognosis of these patients depend heavily on the early detection of metastases. The most effective surveillance strategy has not yet being established. The introduction of second generation ultrasound contrast agents have improved the ability of contrast-enhanced ultrasound (CEUS) in detecting and characterizing liver lesions, showing that its accuracy is comparable to that of spiral CT e MRI with a liver contrast agent, with a cost and a time saving. We are conducting a feasibility study in order to verify the sensitivity and specificity of CEUS in detecting liver metastases compared with the standard imaging modalities used in the follow up of CRC.

Methods: A prospective pilot study considering all patients with a diagnosis of CRC in high risk stage II, stage III or with a previous metastasectomy of the liver. In order to detect possible metastases, the patients were followed with a follow-up schedule including a six-monthly ultrasonography alternated to an annual CT and a six-monthly CEUS with SonoVue contrast agent for the first 3 years.

Results: The accrual was reached with 85 patients enrolled in 2 years. The percentage of liver progression detected was 18%. So far we executed 190 CEUS, identifying 39 suspected liver lesions. The concordance between CEUS and CE-CT was 89% with 35/39 confirmed focal lesions. The percentage of false positive was 7 % with 3/39 benign lesions. The percentage of false negative was less than 4% with 2 /39 lesions resulted positive with additional MRI or CT. CEUS improve specificity and sensitivity compared with baseline ultrasonography. We had an histological confirmation in all cases except one.

Conclusions: Our results are strongly supporting the similar diagnostic performance and confidence of CEUS compared to these imaging modalities in the follow-up of CRC. According to the results of this study we are planning a validation protocol for CEUS as standard technique for liver metastases diagnosis.

Disclosure: All authors have declared no conflicts of interest.

671 COMPARISON OF THE EFFICACY AND TOLERABILITY OF RALTITREXED-BASED CHEMOTHERAPY VERSUS 5-FLUROURACIL-BASED CHEMOTHERAPY IN ASIAN COLORECTAL CANCER PATIENTS

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Background: Physicians have often used raltitrexed based in substitute of 5-fluorouracil-based (5-FU) therapy for patients who are intolerant of the side effects of 5-FU.

Objective: We assessed if raltitrexed-based therapy is of comparable efficacy and tolerability as 5-FU based therapy in Asian colorectal cancer patients.

Methods: This is a large retrospective analysis of 867 consecutive colorectal cancer cases diagnosed between Jan 1988 and Mar 2010 in a single institution. The statistical analyses were carried out with SPSS version 15.0 (SPSS, Inc). The level of significance was set at $P < 0.05$.

Results: 750 patients were on 5-FU based and 117 patients were on raltitrexed based therapy. Median age at diagnosis (5-FU vs raltitrexed: 60.7 vs 62.5 years, p=0.107). There were no significant differences in the demographics of patients receiving 5FU and raltitrexed in terms of gender and race. There is slightly higher proportion of patients age ≥70 on raltitrexed arm (30 vs 22%, p=0.05). A significantly higher proportion of patients with cardiac comorbidities were treated with raltitrexed-based therapy (17% vs 7%, p<0.0001). Median PFS for patients on palliative 5FU is inferior to raltitrexed (11 vs 15 months, p=0.03). OS was superior in 5-FU arm when compared to raltitrexed when given for adjuvant (57.6 vs 46.3 months, p=0.007) and palliative indications (17.7 vs 12.1 months, p=0.005) after adjusting for age, performance status, presence of cardiac comorbidities. Diarrhea was seen more commonly in the raltitrexed arm (31 vs 17%, p=0.05) but there was no significant difference in mucositis and cardiac events.

Conclusion: Our study shows that raltitrexed was well tolerated and did not compromise PFS when compared to 5FU in the palliative setting however the lower OS suggests that its use should be limited to patients who are intolerant to 5FU.

Disclosure: All authors have declared no conflicts of interest.

672 OXALIPLATIN STOP-AND-GO STRATEGY WITH ORAL S-1 MAINTENANCE THERAPY IN ADVANCED COLORECTAL CANCER; CCOG-0704 STUDY

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Purpose: In metastatic colorectal cancer (mCRC), a combination of leucovorin and fluorouracil with oxaliplatin (FOLFOX) is one of the standard first-line regimen. The cumulative neurotoxicity of oxaliplatin often requires therapy to be stopped in patients who are still responding. The aim of this study was to evaluate modified FOLFOX6 (mFOLFOX6) with the intermittent oxaliplatin treatment and maintenance therapy with S-1, oral fluoropyrimidine derivative, in the first-line treatment of mCRC.

Patients and methods: Thirty patients with untreated mCRC were treated with six cycles of mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, 5-fluorouracil bolus 400 mg/m^2 and 5-fluorouracil continuous 2400 mg/m^2, every 2 weeks) followed by maintenance therapy with oral S-1 (S-1 80-120mg/body days 1-28, every 6 weeks). Reintroduction of mFOLFOX6 was scheduled after four cycles of S-1 or tumor progression. The primary study end point was duration of disease control (DDC).

Results: Twenty of the 30 patients (66.7%) who achieved responses or stabilizations received S-1 maintenance therapy. mFOLFOX6 was reintroduced in twelve patients (40.0%). Median DDC was 13.1 months. Median progression-free survival (PFS) was 9.0 months. Overall response rates and disease control rates were 40.0% and 80.0% for the initial mFOLFOX6, 15% and 45.0% for S-1 maintenance therapy and 25.0% and 58.3% for mFOLFOX6 reintroduction. Twenty-eight patients (93.3%) had peripheral neuropathy during treatment, but grade 3 neurotoxicity was observed in only 1 patient (3.3%).

Conclusion: The planned oxaliplatin stop-and-go strategy with oral S-1 maintenance therapy was feasible first-line treatment for Japanese mCRC patients. Further prospective randamized control study is warranted.

Disclosure: All authors have declared no conflicts of interest.

673 A MULTICENTER FEASIBILITY STUDY WITH S-1, OXALIPLATIN AND ORAL LEUCOVORIN (SOL) FOR THE PATIENTS WITH UNTREATED METASTATIC COLORECTAL CANCER : THE RESULT OF INTERIM ANALYSIS

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Background: Previous phase I study with S-1, oxaliplatin and oral leucovorin (SOL) demonstrated well tolerability and efficacy in Japanese patients with metastatic colorectal cancer. The present feasibility study was conducted to confirm the safety and efficacy of SOL in Chinese patients with untreated metastatic colorectal cancer preliminary.

Methods: Eligibility: untreated, unresectable or recurrent advanced colorectal adenocarcinoma, age≥20, ECOG Performance Status (PS) of 0-2, adequate organ functions, and no prior history of chemotherapy, The treatment schedule comprised S-1 40-60mg bid and LV 25mg bid for one week and 2 hour drip infusion of oxaliplatin (L-OHP) 85mg/m2 on day 1, repeated every 2 weeks.

Results: A total of 20 (median age: 65; range: 30-78) were enrolled between August 2009 and December 2009. There were 14 patients with colon cancer and 6 with rectal cancer. Of the 20 patients, 10 were initially diagnosed with metastatic cancer and 10 were relapsed cancer after surgery. Data cut-off date was March 15, 2010. In total, 115 cycles were administered (median 6 per patient; range 1–10). Toxicities and responses were evaluated in 20 patients. The common hematologic toxicities were neutropenia (55%), thrombocytopenia (45%) and anemia (25%). The common non-hematologic toxicities were fatigue (45%), diarrhea (35%), nausea/vomiting (30%),peripheral neurotoxicity (25%). The incidence of any adverse events (grade 3/4) was 40% (8/20), including diarrhea (20%), thrombocytopenia (10%) and nausea/vomiting (10%). Dose-adjusted was executed in 11 patients owing to AEs, including S-1 in 9 cases and L-OHP in 9 cases. Death due to adverse event was not observed. In 20 patients with measurable disease, the overall response rate was 45% (1 CR and 8 PR: 95% CI 23-68%) and the disease control rate was 90%(95% CI 68%-99%). Pathologic complete response was observed in 1 patient after 5 cycles of treatment. Median PFS was not reached.

Conclusions: This preliminary result indicates that the SOL regimen is well tolerated and effective in Chinese patients with metastatic colorectal cancer.

Disclosure: All authors have declared no conflicts of interest.

674 RELATIONSHIP BETWEEN MRNA EXPRESSION LEVELS AND CLINICAL EFFICACY OF ORAL URACIL AND TEGAFUR/ LEUCOVORIN CHEMOTHERAPY IN PATIENTS WITH COLORECTAL CANCER

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Background: 5-Flurouracil (5-FU)/ leucovorin (LV) and oral uracil and tegafur (UFT)/ LV are widely used as standard adjuvant chemotherapy for colorectal cancer (CRC). We previously reported that folylpolyglutamate synthase (FPGS) and g-glutamyl hydrolase (GGH) were associated with the reduced folate levels in CRC tissues after LV administration. In the present study, we examined the relationship between mRNA expression of pyrimidine and folate metabolism-related enzymes in CRC tissues and the efficacy of UFT/LV treatment.

Material and methods: Twenty CRC patients without prior treatment who were scheduled to undergo surgery were enrolled. They received oral UFT/LV for 2 weeks until 2 days before surgery. We evaluated the tumor response based on the endoscopic appearance and on pathologic regression of the resected specimens. The endoscopic appearance was evaluated using 4 categories (0 ~ 3+). A response based on the endoscopic appearance was defined as a category of 2+ or greater. The pathologic regression was evaluated using 5 categories according to the Japanese criteria(0, 1a, 1b, 2, and 3). A response based on the pathology was defined as a category of 2 or greater. The mRNA expressions of pyrimidine-related enzymes and folate-related enzymes were quantitatively evaluated using a RT-PCR assay. The evaluation of predictive factors was based on differences in the mRNA expression levels between responders and non-responders.

Results: Tumor responses based on endoscopic appearance and the pathologic regression were observed in 50% (10/20) and 25% (5/20), respectively. The respective median FPGS mRNA expression values were 0.97 and 0.70 for responders and non-responders based on the endoscopic appearance. This difference was marginally significant (P = 0.070). No differences between the other mRNA expression levels and the response were observed. However, when combined with thymidylate synthase (TS), the respective median FPGS/TS ratios were 2.23 and 1.38 for responders and non-responders , and this difference was significant (P = 0.023).

Conclusion: The combination of FPGS and TS mRNA expression levels in primary tumors may be useful for predicting the efficacy of oral UFT/LV treatment in patients with colorectal cancer.

Disclosure: All authors have declared no conflicts of interest.

675 CORRELATION OF BRAF STATUS WITH CLINICAL RESPONSE TO CETUXIMAB IN KRAS WILD TYPE (KRAS WT) METASTATIC COLORECTAL (MCRC) PATIENTS - SINGLE INSTITUTION EXPERIENCE

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Background: KRAS mutation status in codon 12 and 13 is recognized as a predictive factor for resistance to anti- EGFR monoclonal antibodies. Other mechanism of resistance could involve activating mutations of the other main EGFR effector pathway. In recent clinical studies, it was published that BRAF wild type (wt) is required for response and that the patients (pts) with BRAF mutation had significantly shorter PFS and OS than BRAF wt pts. We retrospectively analyzed BRAF status in KRAS wt mCRC patients treated with chemotherapy (ChT) in combination with cetuximab.

Methods: The pts with mCRC were tested for KRAS mutations in codons 12 and 13, and treated with standard ChT in combination with cetuximab according to KRAS wt status. BRAF analysis of mutation in codon 600 was retrospectively determined by quantitative PCR.

Results: From September 2008 to December 2009 54 pts with KRAS wt were treated with ChT in combination with cetuximab, 51 of them in first-line therapy. Most of pts received ChT with oxaliplatin in combination with fluoropyrimidines (XELOX/ XELIRI/ FOLFOX/FOLFIRI in 25/19/6/4 pts respectively). BRAF V600E mutation (mut) was detected in 7 pts (12.9 %). Response rates in BRAF wt pts were: CR 21.2%, PR 36.2%, SD 29.8%, PD 12.8%. TTP was 11.7 months (95% CI: 10.7-12.8 months), at the time of analysis median TTP was not reached. Response rates in BRAF mut pts were: CR 0%, PR 0%, SD 14.3%, PD 85.7%. Six of 7 BRAF mut pts progressed early during therapy, median TTP was 4.2 months.

Conclusions: Results of our small retrospective analysis suggest that the pts with BRAF mut have worse prognosis than the pts with BRAF wt and progress rapidly during treatment and that BRAF wt is required for response to ChT in combination with cetuximab. The definitive role of BRAF mut as a prognostic and predictive factor to response anti-EGFR monoclonal antibodies needs to be analyzed in large prospective clinical studies.

Disclosure: All authors have declared no conflicts of interest.

676 PHASE II STUDY OF COMBINATION CHEMOTHERAPY WITH BIWEEKLY CETUXIMAB AND IRINOTECAN FOR WILD-TYPE KRAS METASTATIC COLORECTAL CANCER REFRACTORY TO IRINOTECAN, OXALIPLATIN, AND FLUOROPYRIMIDINES

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Background: Weekly cetuximab and irinotecan is a standard regimen in heavily pretreated patients with metastatic colorectal cancer (MCRC). The aim of this study was to prospectively evaluate the efficacy of combination chemotherapy with biweekly cetuximab and irinotecan in patients with pretreated MCRC harboring wild-type KRAS.

Patients and methods: Patients with wild-type KRAS MCRC that had progressed after chemotherapy with irinotecan, oxaliplatin, and fluoropyrimidine were included in this study. Cetuximab was administered at 500 mg/m^2 biweekly with irinotecan. The primary endpoint was response rate. The secondary endpoints included adverse events, progression-free survival, and overall survival. The pharmacokinetics of cetuximab was also evaluated in 5 patients.

Results: From May, 2009 to February, 2010, a total of 31 patients were enrolled from five institutions. One patient was not eligible. Among the 30 assessable patients, ECOG PS was 0 in 12, 1 in 16, and 2 in 2 patients. The objective response rate was 30.0% (95% confidence interval [CI], 14.7-49.4), and the disease control rate (complete response, partial response, or stable disease) was 76.7% (95%CI, 61.4-92.3). The median progression-free survival was 5.3 months (95%CI, 3.4-7.3) with a median follow up time of 6.3 months. Grade 3 skin toxicity was observed in 2 patients (8%), and treatment related death due to pneumonia occurred in one patient.

Conclusions: The efficacy data are similar to those of standard dose of cetuximab plus irinotecan. Combination chemotherapy with biweekly cetuximab and irinotecan is effective for pretreated metastatic wild-type KRAS MCRC.

Disclosure: All authors have declared no conflicts of interest.

677 BEVACIZUMAB IMPROVES PATHOLOGIC RESPONSE IN PATIENTS TREATED WITH OXALIPLATIN-BASED CHEMOTHERAPY FOR COLORECTAL LIVER METASTASES: REPORT FROM A RETROSPECTIVE STUDY

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Aim: Histological response of liver colorectal metastases (LCM) to ChT may be graded and has been correlated with survival. The purpose of the study was to evaluate the pathological response and the ChT-induced hepatic injury after resection of LCM in patients treated with neoadjuvant ChT with or without bevacizumab (BV).

Methods: Forty consecutive patients were evaluated retrospectively. We compared the histological response in patients treated with ChT plus BV (Group A; N:14) or with cChT (Group B; N:9). The response to the treatment was evaluated by pathological analysis of tumour viability (Grade 1: no residual tumour; Grade 2: minimal residual cancer; Grade 3: moderate response; Grade 4: no definitive response identified). Liver injury was investigated, scored between 0 and 3 and compared with control-group of patients operated without neoadjuvant treatment (Group C; N:17).

Results: Groups were comparable for gender, pT, pN and primary tumour location (colon vs rectum). Patients from groups A-B were younger (59.8 vs 57.7 vs 68.7 years; p=.002), had a higher rate of synchronous metastases and a higher number of metastases than patients from Group C. Patients treated with ChT + BV had higher rates of good histological response (Grades 1-2) than patients treated with ChT alone (78% vs 44%; p=.034). Patients with a good histological regression had a non-significant benefit in overall survival over patients with a poor response (33.5 vs 26.8 months; p.328). No significant difference was found in the three groups with respect to sinusoidal dilation (p=.782) or steatosis (p.067).

	Group A	Group B	Group C	p-value
Synchronous metastases	71.4%	77.7%	35.2%	0.45
Median number metastases	4.8	4.5	1.7	0.002
Median survival (months)	33.5	26.8	36	0.200
Histological response 1-2	78%	44%		0.034

Conclusion: The addition of BV to ChT prior to resection of LCM provides a better histological regression rate compared with ChT alone. Good responder patients had a tendency to benefit in overall survival. In our series, no significant ChT-induced hepatic injury was found.

Disclosure: All authors have declared no conflicts of interest.

678 BEVACIZUMAB IN COMBINATION WITH CHEMOTHERAPY IN METASTATIC COLORECTAL CANCER - THE MCGILL EXPERIENCE

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Background: Bevacizumab (BV) prolongs overall survival (OS) and progression-free survival (PFS) when added to standard chemotherapy (CT) for metastatic colorectal cancer (mCRC). After approval of BV in Canada in 2005, this observational cohort study was designed to include patients (pts) receiving various CT regimens with BV in order to evaluate its safety and efficacy.

Methods: Eligibility criteria were minimized to facilitate enrolment of a typical mCRC population. Choice of the CT regimen was at physicians' discretion. Predefined endpoints were treatment characteristics, PFS, OS stratified by line of therapy that BV was initiated, and grade 3-4 adverse events (AE) likely related to BV. Pts were followed for up to 4 years, and clinical data updated every 3months.

Results: 196 eligible pts were enrolled at a single centre from April 2005 to Dec 2007. Median age: 55 (range 18-79), age >70: 12%; male 55%; ECOG PS status 0-1/2/>2 95%/5%/0%. First line CT choice (49% of pts) was oxaliplatin-based 55%, irinotecan-based 43%, or combined oxaliplatin-irinotecan 2%. Second line CT choice (22% of pts) was oxaliplatin-based 39%, irinotecan-based 60%, or combined oxaliplatin-irinotecan 1%. Third or greater line CT choice (25%) of pts was oxaliplatin-based 25%, irinotecan-based 65%, or combined oxaliplatin-irinotecan 6%. In total, 37 AE were reported: thrombocytopenia in 8.6% of pts, venous thromboembolism 4.6%, hypertension 1.5%, bleeding 1.5%, bowel perforation 1.0%, nephrotic syndrome 0.5%, posterior reversible leukoencephalopathy syndrome 0.5%, and allergic reaction 0.5%. First line median PFS=10months (m), median OS=52m. Second line median PFS=6.5m, median OS=60m. Third line or greater median PFS=5.5m, median OS=58m.

Conclusions: The safety profile of BV in this population of mCRC pts with different CT regimens is consistent with that observed in patient registries/nonrandomized trials (e.g., BEAT or BRiTE). Median PFS and OS in first line therapy was very similar to that reported in previous trials, with diminishing benefits in PFS associated with later introduction of BV.

Disclosure: All authors have declared no conflicts of interest.

679 RELEVANT: PROSPECTIVE EVALUATION OF EFFICACY AND SAFETY OF BEVACIZUMAB THERAPY IN METASTATIC COLORECTAL CARCINOMA; INTERIM ANALYSIS OF RESECATABILITY RATE

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Background: Bevacizumab with XELOX/FOLFOX is a standard treatment option for metastatic colorectal cancer (CRC). Resection of liver metastases may be the best choice for improving survival for these patients. Prior neoadjuvant therapy may allow that patients with initially unresectable liver metastases become resectable.

Method: This is interim analysis which assessed response rate (RR) for Bev+ CAPOX/FOLFOX in pts considered unsuitable for upfront resection of liver-only metastases. Eligible pts had unresectable liver-only mets (synchronous: N= 4 or metachronous: N= 6) or potentially resectable liver-only mets diagnosed synchronously with the primary tumour N= 5 or metachronously N=16, according to surgical assessment. Resectability was reassessed after every 4 cycles of CAPOX/FOLFOX+Bev.

Results: Until now, 63 patients has been recruited into study and have started treatment. Based on current evaluated data, assessment after 4 cycles of CAPOX/FOLFOX+ Bev resulted in clinical benefit (CR+PR+SD) of 83,4% (excluding 1 pts without response rate, NA). 2 pts with CR, 9 with PR, 14 SD and 5 pts with PD. 10/31 pts had unresectable disease at entry. Clinical benefit was achieved in 8/10 (80%); 2/10 pts had progression of disease. 4/10 (40%) have been converted to resectable and proceeded to surgery. 21/31 pts had potentially resectable liver mets at entry. Clinical benefit has been achieved in 17/21 (81%) and 10/21 (47,6%) have been proceeded to surgery; 6/21 are continuing CAPOX/FOLFOX+Bev or awaiting surgery and one has been additionally selected for resection. In total 15/31 (48,4%) pts have been proceeded to surgery. Specific grade 3/4 Bev-related toxicities were: hypertension- 3,2%, venous thromboembolism- 3,2%.

Conclusion: In pts with initially unresectable or potentially resectable liver-only CRC mets, CAPOX/FOLFOX+bev is associated with a high respectability rate of 48,4% after only 4 cycles of treatment. At least 40% of unresectable pts have been downstaged to resectable and 47,6% of potentially resectable became resectable. Updated results to be presented.

Disclosure: All authors have declared no conflicts of interest.

680 FOLFIRI VS FOLFIRI + BEVACIZUMAB IN FIRST-LINE THERAPY OF METASTATIC COLORECTAL CANCER: RETROSPECTIVE ANALYSIS OF 81 PATIENTS IN OUR INSTITUTION

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Background: Neoadjuvant chemotherapy is standard of care for metastatic colorectal cancer. Bevacizumab prolongs pregression-free survival (PFS) and median survival when added to chemotherapy for first-line treatment of patients with metastatic colorectal disease.

Methods: We retrospectivly analysed 81 patients with metastatic colorectal cancer who were treated in our institution from April 2007. to October 2009. The aim of this study was to access progression-free survival and evaluate toxicity of therapy. There were 49 male and 32 female patiens. As first line of chemotherapy for metastatic disease 37 patiens received FOLFIRI in standard doses (Group I) and 44 FOLFIRI + bevacizumab 5mg /kg (Group II). Mean age was 63.3 ± 9.8 (Group I) and 59.7 ± 9.8 (Group II), p=0.101. The most frequent site of metastatic disease was liver, 64.9% (Group I) and 72.7% (Group II), p=0.445. ECOG status was 0 (51.4%) and 1 (48.6%) in Group I, 65.9% and 34.1% in Group II, respectively, p=0.143.

Results: Average number of applied cycles was for FOLFIRI 9.6 ± 4.9 and for FOLFIRI + bevacizumab 13.6 ± 5.3, p=0.001. Confirmed time to progression for FOLFIRI (Group I) was 6.9 months and for FOLFIRI + bevacizumab (Group II) 10.2 months, p=0.003. In multivariate analisys (age, gender, ECOG status, site of metastatic disease, type of therapy) only significantly associated factor to outcome of treatment was type of therapy. Addition of bevacizumab to FOLFIRI showed improvement in PFS, HR=0.40, 95% CI 0.21-0.78, p=0.007. The most common side-effects in both groups were diarrhea, nausea, vomiting and neutropenia, but without statistically significant difference between groups. In Group II (FOLFIRI + bevacizumab) there were two tromboembolic events (4.5%), one intestinal perforation (2.3%), one bleeding from primary (2.3%), hypertension in four patients (9.0%).

Conclusions: Our data suggest that combination of FOLFIRI + bevacizumab is signifficantly better combination than FOLFIRI in term of PFS, with acceptiable toxicity.

Disclosure: All authors have declared no conflicts of interest.

681 NEUTROPENIA AND GENDER DIFFERENCIES AT LIVER-ONLY METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH OXALIPLATIN-BASED NEOADJUVANT CHEMOTHERAPY PLUS BEVACIZUMAB: IS THERE ANY IMPACT ON RESECTION RATE?

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Introduction: Combined chemotherapy (cytotoxics+biological agent) that aimed to shrink liver metastases and to allow successful resection may be associated with haematological toxicity in colorectal cancer (CRC) patients (pts). In general, neutropenia is not an obstacle for resection planning, but it may prolong chemotherapy period and possibly affect further steps in this potentially curative setting.

Methods: Pts with potentially resectable liver-only metastatic CRC and PS 0/1 have been selected to receive at least four induction cycles of FOLFOX4 regimen (or XELOX) + bevacizumab, at the Institute for Oncology and Radiology of Serbia, since Sep 2008. Neutropenia and delay in chemotherapy delivery with G-CSF support (in days) were recorded. Response rate (RR) and resection rate were analyzed.

Results: Forty-seven pts were assessed for resection. Thirty-eight pts received four or more cycles of FOLFOX4 (six of them XELOX) + bevacizumab, nine pts received up to four cycles of the same therapy. Among these 47 pts 21 were male, 26 female, median age was 56 years, and PS 0 was recorded in 41/47 (87%) pts. Febrile neutropenia was not registered, grades 3 and 4 neutropenia were recorded in 40% of pts, (male vs female: 29% vs 50%, p=0.08). Median delay in chemotherapy administration and G-CSF consumption was 3 days (males/females:4/3). RR was 38%, both in males and females. Overall resection rate was 26% (12/47 pts), in male pts14 %(95%CI: 5-35%), in female pts 35%(95%CI:19-54%), p=0.18. Higher grades of neutropenia did not significantly impact resection rate: among 19 pts who experienced grades 3 and 4 neutropenia 7 pts were resected, among 26 pts with grades 0-2 neutropenia 4 pts were resected, p=0.16. At pts with neutropenia grades 3 and 4 response rate was 58%, while at pts with neutropenia grades 0-2 response rate was 19%, p=0.004.

Conclusion: It appears that moderate and severe neutropenia, although experienced in 40% of pts after the induction of four cycles of chemotherapy + bevacizumab, did not affect the planned further treatment. There was no proof of gender differencies significance. These preliminary findings deserve further studies, in order to understand better prognostic and predictive factors in setting of liver-only metastatic CRC.

Disclosure: All authors have declared no conflicts of interest.

682 COLORECTAL CANCER PATIENTS PROFILE AND BENEFIT TO BEVACIZUMAB TREATMENT BASED REGIMENS: THE RESULTS OF A ROMANIAN LOCAL OBSERVATIONAL STUDY (PEPSACO)

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Background: PEPSACO is the first local, observational study, started in Romania to explore the tolerability profile and efficacy of bevacizumab (BV) used in daily clinical practice in patients (p) with metastatic colorectal cancer (mCRC).

Methods: Between 2007 and 2009, 88p with mCRC were treated with BV based regimens. For each administration, was assessed the tolerability to BV perfusion based on medical judgement including ECOG patient clinical status, hypertension, proteinuria and other adverse events (AEs) that were collected until the end of the study. The secondary endpoint was progression free survival (PFS) for the first line of therapy.

Results: Patients' characteristics were: mean age:54.3y, 16p (18.1%) older than 65,sex:M/F 49/39,primary tumour location:colon 53p(60%), rectum 33p (37.5%), and both 2p (2.5%),previous therapies:surgical resection: 83p (94.3%), adjuvant therapy: 44 p(50%) and radiotherapy: 11p(12.5%). Synchronous M1 in 40 p (45.5%) and metachronous in 48 p (54.5). Metastases (M1): 1 site at 67p: liver M1 at 63p and lung M1at 4p; 2 sites of M⊂1 at 15 p and > 3 sites at 6 p. 19 p had surgical resection of liver M1.20 p (22.7%) were treated with 2lines of chemotherapy with BV. A very good tolerability to BV was observed at 86% of the p. The median PFS calculated using Kaplan-Meier method was 13.8 months (95% CI 11.2,16.5).PFS was compared between subgroups of p depending on location of the primary tumour and synchronous vs. metachronous M1 using the log rank test. Results showed that even if p with primary tumour of the rectum seemed to have a better PFS, the results were not statistically significant. There were no differences between the synchronous and metachronous groups of patients in our study.

Conclusion: The efficacy of BV in mCRC was confirmed in daily clinical practice.

Disclosure: All authors have declared no conflicts of interest.

683 CLINICAL OUTCOMES IN METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH BEVACIZUMAB AND K-RAS MUTATION STATUS

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Introduction: Mutations of the K-ras gene were identified as a negative predictor of clinical benefit from anti– epidermal growth factor receptor treatment in metastatic colorectal cancer (mCRC). Previous data, from clinical trials, suggest that the clinical benefit in patients treated with Bevacizumab plus chemotherapy is independent of alterations in the Ras/Raf/Mek/Erk pathway. We were aimed to investigate the impact of K-ras mutational status in clinical outcomes – progression free survival(PFS) and overall survival(OS) - of patients with mCRC treated with Bevacizumab plus chemotherapy in a unselected population.

Patients and methods: A retrospective analysis of our patient's dataset with mCRC treated with Bevacizumab plus chemotherapy after May 2006 in our institution was performed. K-ras mutation status was analyzed by RT-PCR in Genomed (IMM) and patients were grouped as having or not K-ras mutation. The PFS and OS times were compared. Multivariate analysis was done with Cox regression model. Log-Rank test was used to determined significance ($p < .05$). We analyzed a population of 70 patients: female:44,8%,male: 55,2%. Median age of diagnosis: 63±8.3 years. K-ras mutation status: mutated: 56,7% (n=38); wild-type: 43,3% (n=29).

Results: The estimate mean PFS with Bevacizumab plus chemotherapy regimens was not significantly different in Bevacizumab-treated patients with wild-type (wt) and mutant (m)-K-ras (10 versus 16 months, p= .053), although a trend was observed to better median PFS in the mutant group. The estimate mean OS after metastatic disease was also not significantly different in Bevacizumab-treated patients with wild-type (wt) and mutant (m)-K-ras (45,3 vs 40,9 months, p=.63). The multivariate analysis showed that K-ras mutational status is not associated with significant different time of PFS or OS after metastatic disease. Patients with liver-only or lung-only mCRC had a better PFS and OS compared with patients with multiple sites of metastatic disease.

Conclusion: The efficacy of chemotherapy plus Bevacizumab is independent of K-Ras mutation status. Patients with liver-only or lung-only metastatic disease have better outcomes with chemotherapy plus Bevacizumab.

Disclosure: All authors have declared no conflicts of interest.

684 EFICACY AND SAFETY OF FOLFIRI-BEVACIZUMAB FOR THE SECOND-LINE TREATMENT OF METASTATIC COLORECTAL CARCINOMA

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Aim; During the course of colorectal carcinoma 40-50% of patients develop metastasis and 50-80% of metastatic colorectal carcinoma (MCRC) patients are ordered a second-line therapy. Herein, we aimed to evaluate the efficacy and the safety of FOLFIRI-B in the second line therapy of metastatic colorectal carcinoma.

Patients and methods: Between March 2006 and July 2009 the data of 35 patients with MCRC that were treated with FOLFIRI-B (irinotecan 180 mg/m^2 D1, folinic acid 200 mg/m^2 D1, 5 FU 400 mg/m^2 iv bolus D1, 5 FU 2600 mg/m^2 46 hours infusion after bolus, bevacizumab 5mg/kg D1, every 2 weeks) at the second line were collected.

Results: The median age of the 35 patients was 54 (36-75). One patient (2.8%) was treated with oxaliplatin including chemotherapy on the adjuvant basis and 33 patients (94.3%) were exposed to oxaliplatin in the first line therapy of MCRC. The median follow up period was 11 months (2-34). Complete remission (CR) was held in 5.7% of the patients and the total of complete and partial remission (PR) was 11.4%. Disease control (the sum of CR, PR and stable disease) was held in 74.3% of the patients. During the follow up period, progression was seen in 32 (91.4%) patients and 23 (65.7%) patients died. The median progression free survival was 7 months (95%CI, 5.1 - 8.9), median overall survival was 12 months (95%CI, 8.5 – 15.5). Grade 3-4 toxicity requiring delay of chemotherapy was observed in 12 (34.3%) patients; 10 (28.6%) had neutropenia and 2 (5.7%) had diarrhea.

Conclusion: FOLFIRI-B may be an efficient and safe choice in the second line for the treatment of patients with MCRC that were previously treated with oxaliplatin.

Disclosure: All authors have declared no conflicts of interest.

685 THE RELATION BETWEEN ENDOGLIN (CD105), THROMBOSPONDIN-1 AND VEGFR-3 AND TREATMENT RESULTS IN METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH BEVACIZUMAB COMBINATION THERAPY

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Background: Angiogenesis is an important step in growth of malignant tumors. The relationship between efficacy and angiogenic factors such as CD105 (endoglin), thrombospondin-1 (TSP-1) and vascular endothelial growth factor receptor-3 (VEGFR-3) in patients with metastatic colorectal cancer (MCRC) treated with bevacizumab, antiangiogenic agent, combination chemotherapy were assessed.

Patients and methods: The clinicopathological data of 42 MCRC patients retrospectively analyzed. The expressions of CD105, TSP-1 and VEGFR-3 were examined in paraffin block of these patients by immunohistochemical staining. Patients had bevacizumab in combination with FOLFIRI, IFL, irinotecan only and FU/LV regimens.

Results: Forty two patients with a median age of 55 years (range, 29-78) were evaluated. The median follow-up was 16 months (range, 3.3-41). The expression of TSP-1 and VEGFR-3 were 11.9% and 19%, respectively and 46% of patients showed widespread expression of CD105. The overall response rate, PFS and OS results according to treatment-line, CD105, TSP-1 and VEGFR-3 expressions as follows: in firs-line, 16.7%, 5 months and not reached and in salvage therapy, 26.7%, 6 and 15 months; in CD105 widespread staining group 13.3%, 6 and 10 months and in CD105 weak staining group 31.6%, 6 and 19 months; in TSP-1 positive group 0%, 6 and 13 months and in TSP-1 negative group 29.7%, 6 and 16 months; in VEGFR-3 positive group 12.5%, 6 and 15 months and in VEGFR-3 negative group 26.5%, 6 and 16 months, respectively.

Conclusion: Non-significant treatment efficacy according to expression of these angiogenic markers in patients treated with bevacizumab combination chemotherapy showed that they have no clinically applicable prognostic significance in MCRC patients. Large prospective studies were necessary to establish this relationship clearly.

Disclosure: All authors have declared no conflicts of interest.

686 ANTIANGIOGENIC THERAPY OF METASTATIC COLORECTAL CARCINOMA – RESULTS FROM TWO CENTRES

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Background: Antiangiogenic treatment with bevacizumab is a part of standard systemic therapy for metastatic colorectal cancer (mCRC). In a retrospective study, we have analysed the outcomes of therapy and prognostic/predictive factors in patients (pts) treated in two Czech cancer centres.

Patients and methods: The cohort included 238 consecutive pts treated with bevacizumab for mCRC at the Masaryk Memorial Cancer Institute and at the Thomayer University Hospital, Czech Republic. The following potential prognostic/predictive factors were evaluated: age, gender, tumour grade, number of metastatic sites, associated chemotherapy regimen, presence/absence of KRAS mutation, and preexisting or therapy-induced hypertension.

Results: Median age of pts treated with bevacizumab as a part of first-line systemic therapy was 60 years. The progression-free survival (PFS) and overall survival (OS) were 11.3 months and 30.6 months, respectively. ORR was 45.6% with 12% CRs and disease stabilisation occurred in 29% of pts. Higher grade and/or number of metastatic sites were adversely associated with both PFS and OS. KRAS was not predictive of PFS but was a strong favourable prognostic factor for OS due to the possibility of subsequent therapy with cetuximab (43.8 vs. 27.5 months, p=0.015). Toxicity profile was as expected but thromboembolic events occurred in as many as 11% of pts 65 years or older. Preexisting or de novo hypertension was not associated with treatment outcomes.

Conclusions: Outcomes of 'real-life' pts with mCRC are comparable to those achieved in clinical trials. Thromboembolism emerges as the most significant toxicity in elderly mCRC pts treated with bevacizumab. Sequential targeted therapy improves survival in mCRC but is currently an option only for pts with KRAS wt tumours.

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All other authors have declared no conflicts of interest.

687 IMPLICATIONS OF EXPRESSION MARKERS OF APOPTOSIS IN COLORECTAL CANCER WITH METASTASIS IN LIVER

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Aim: To demonstrate correlation dependence between levels of expression of p53 and bcl-2 in patient's with colorectal cancer (CRC) metastasis in liver and the results of using chemotherapy.

Materials and methods: Study was of 83 CRC patients with metastasis in liver. 1st group (n=32) receiving chemotherapy by the FOLFIRI regimen (irinotecan-180 mg/m^2, leucovorin-200mg/m^2, fluorouracil-400mg/m^2 intr.v. jet in 1st day , than 5FU – 2.4 – 3.0g/m^2 24 hours intr.v. infusion.), 2nd group (n=25) regional endovascular chemotherapy (RECH) with 5-fluoruoracil– 1000 mg/m^2 daily during 72 hours and oxaliplatin 100 mg/m^2 daily during 16-18 hours on the fourth day, 3rd group (n=26) received capecitabine (Xeloda; 35000 mg/m^2). All patients were subject to immunohistochemical analysis of expression of protein p53 and bcl-2 using DAB (Dako Cytomation).

Results and discussion: results showed that the highest level of protein expression of mt p53 in tissue of primary tumor (n=20) was found in moderately differentiated adenocarcinoma. In high-grade differentiated adenocarcinoma the expression p53 occurs in 52.0%, in moderately differentiated adenocarcinoma in 41.66%. Immunohistochemical analysis of primary tumor CRC showed 35 (42.1%) cases of gene expression of mt p53, of them in 10 (12.04%) showed high expression of the given oncoprotein. Absence of gene expression mt p53 was observed in 57.83% patients. Expression of bcl-2 was negative. Analysis of results showed that the conducted treatment results were dependent on patient phenotype. Using FOLFIRI showed full regression (single metastasis in lungs) in 2 patients (6.25%). Partial regression using FOLFIRI was observed in 70 %, and in RECH-in 41.67% of patients, in positive expression of p53 this rate goes down till 23.1%. Using capecitabine showed partial regression of tumor in 23.54% patients, in positive regression mt 53 this rate goes down till 11.12%.

Conclusion: The conducted research showed that expression of p53 is a negative factor in the process of carcinogenesis, increasing poor prognosis and decreasing the effect of using traditional schemes of chemotherapy. Treatment of patients with metastasis in liver of CRC with FOLFIRI allowed the drug resistance of tumor cell to be overcome, and achieved effective treatment in 71.97% patients.

Disclosure: All authors have declared no conflicts of interest.

688 EXPRESSION AND CLINIC AND PROGNOSTIC SIGNIFICANCE OF PTEN, P53, VEGF AND CERB-B2 IN METASTATIC COLORECTAL CANCER TREATED WITH BEVACIZUMAB

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Abstract Background: The tumour suppressor phosphatase and tensin homolog (PTEN) is an important negative egulator of cell-survival signaling. VEGF and Cerb-B2 are proliferative proteins that stimulated in carcinogenesis and also p53 protein especially it's mutation is presented in majority of colorectal cancer patients. To evaluate the correlation between PTEN, VEGF, p53 and Cerb-B2 expression and clinicopathological characteristics of colorectal cancer patients with metastases who treated with bevacizumab, we investigated the the clinic and prognostic significance of those proteins and also correlation with each other, respectively.

Methods: Thiry-four patients of primary colorectal cancer and with metastasis were analyzed immunohistochemically, and the correlation between immunohistochemical findings and clinicopathological factors was investigated.

Results: PTEN was expressed in 22 (64%), VEGF expressed in 23 (67%), p53 expressed in 18 (52%) and Cerb-B2 was expressed in 6 (17%) patients respectively. In detailed analysis, tumor grade was strongly correlated with trend to metastasis (p=0.001), perineuronal invasion (p=0.000) and lymphovascular invasion (p=0.001). The cases highly expressed VEGF were significantly correlated with trend to metastasis (p=0.028) and Cerb-B2 (p=0.05) PTEN expression was correlated with lymphovascular invasion (p=0.077) and p53 expression (p=0.052) and p53 expression was negatively correlated relapsed time (p=0.054), respectively. All of the expresed proteins were not correlated with bevacizumab therapy responce. In terms of survival high tumor grade, VEGF expression and p53 expression were determined the time to progresion without independent effect of PTEN expression.

Conclusion: Our results suggest that loss of PTEN, VEGF, p53 expression were involved with colorectal cancer carcinogenesis and did not determined bevacizumab therapy responce, and lymphovascular invasion, tumor grade remains the main prognostic criteria of colorectal cancer.

Disclosure: All authors have declared no conflicts of interest.

689 PHASE II STUDY OF OXALIPLATIN AS THIRD-LINE CHEMOTHERAPY IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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Purpose: This is phase II study to evaluate tumor response rate and safety profile of oxaliplatin when administered to patients in 3rd line setting metastatic colorectal adenocarcinoma.

Patients and methods: A total of 33 patients were enrolled in this study. All patients received 5-FU and LV in 1st line and Irinotecan+5-FU+LV or Capecitabine+5-FU as 2nd line setting. Two patients was excluded, one for having had a second cancer and another one for discontinuation of treatment, so the study was based on 31 patients. Patients were treated with oxaliplatin 130 mg/m2 as a 2-hour infusion on day 1, every 21 days for average 9 cycles (Range 6 – 12).

Results: Ten partial responses (PRs) were observed (response rate, 32.25%; 95% confidence interval, 11.8% to 41.2%). The median duration of response was 120+ days. Fifteen patients (48.38%) had stable disease and 5 (16.1%) had progressive disease. The median progression-free survival time for all patients was 75+ days (range 21 to 132+). The main toxicity was peripheral sensory neuropathy. Grade 3 neurotoxicity was reported in 32%. Hematologic and gastrointestinal toxicities were mild. The incidence of grade 3 neutropenia was 17.2%, while that of grade 3 or 4 thrombopenia was 8.9%. Vomiting (grade 3 or 4) occurred in 15.1% of patients and grade 3 diarrhea in 2.6%.

Conclusion: This phase II study clearly shows the evidence of the safety and efficacy of oxaliplatin monotherapy at this dose and schedule in patients with metastatic colorectal carcinoma as 3rd line setting.

Disclosure: All authors have declared no conflicts of interest.

690 MITOMYCIN-C, 5-FLUORORACIL, AND LEUCOVORIN AS A SALVAGE THERAPY IN PATIENTS WITH METASTATIC COLORECTAL ADENOCARCINOMA

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Background: There was no further treatment option for metastatic colon patients who were refractory to standard chemotherapy and not available to biologic novel agents. We evaluated the outcomes of mitomycin-C/5-FU/leucovorin in patients with

metastatic colon cancer receiving previously oxaliplatin/5-fluorouracil(FU)/leucovorin (FOLFOX) and irinotecan/5-FU/leucovorin (FOLFIRI). Methods We retrospectively analyzed 46 patients who had received mitomycin-C/5FU/leucovorin between March 2008 and December 2009. All patients had failed prior first-line and second-line therapy containing oxaliplatin, irinotecan and 5-fluorouracil.

Results: The median age of patients was 57.0 years (range, 34.0-76.0) and median ECOG PS was 1 (0-2). In all patients, complete or partial response was not observed and stable disease was observed in 19 patients (41.3%). The median duration of follow-up was 29.14 weeks (range 7.71-87.29 weeks). The median progression free survival (PFS) was 10.14 weeks (95% C.I. 8.45-11.83) and the median overall survival (OS) was 38.00 weeks (95% C.I. 32.28-43.72). Grade 3 and 4 hematologic toxicities included neutropenia in 5 patients (10.8%) and thrombocytopenia in 4 patients (8.8%). Grade 3 or 4 non-hematologic toxicities included nausea and vomiting in 2 patients. There were no treatment related deaths.

Conclusion: The combination regimen of mitomycinC/5-FU/leucovorin showed marginal activity and tolerable toxicity profiles in heavily pretreated metastatic colorectal cancer patients.

Disclosure: All authors have declared no conflicts of interest.

691 MULTICENTER PHASE II STUDY OF FOLFOX6 AS NEOADJUVANT CHEMOTHERAPY FOR PATIENTS WITH UNRESECTABLE LIVER-ONLY METASTASES FROM COLORECTAL CANCER IN JAPAN; ROOF STUDY

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Background: A phase II multicenter cooperative study was conducted in 38 medical institutions using modified FOLFOX6 (mFOLFOX6) as neoadjuvant chemotherapy from January 2008 to Jun 2009.

Patients and methods: Patients with liver-only metastases from colorectal cancer deemed not optimally resectable by surgeons received mFOLFOX6 (oxaliplatin 85mg/m2, bolus 5-FU 400mg/m2, leucovorin 400mg/m2 day1 followed by 46-hour infusion 5-FU 2.4mg/m2) as neoadjuvant therapy for 6-8 cycles. Unresectable liver metastases was defined as >4 metastatic tumors and/or a tumor >5 cm in maximum diameter. Patients were reassessed for resectability after 6 cycles of mFOLFOX6. Surgery was carried out 3-6 w after chemotherapy . Primary end point was macroscopic curative surgery including liver resection.

Results: 36 patients (23M/13F, ECOG PS 0-1) were enrolled . Median age of the patients was 62.5 years, 78% (28 patients) had 5 or more metastatic tumors, 53% (19 patients) had metastatic tumors in over 5cm diameter. Modified FOLFOX6 regimen was safety administered resulting in 18 PRs (50%), 12 SDs, and 4 PDs. There was no grade 3/4 neurotoxicity. Fifteen patients (42%) underwent surgery (R0;13, R1;2). There were no treatment-related deaths. 31 patients are alive after a median follow-up of 12 months (range 3-24 months).

Conclusion: Our data suggest that mFOLFOX6 has a high response rate in patients with liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a portion of patients initially not judged to be optimally resectable. Updated efficacy and safety data will be presented.

Disclosure: All authors have declared no conflicts of interest.

692 COLORECTAL (CR) RESECTABLE LIVER METASTASES: LONG-TERM PATIENT SURVIVAL AFTER PREOPERATIVE TRANSARTERIAL CHEMOEMBOLIZATION (TACE) WITH OXALIPLATIN FOLLOWING HEPATIC RESECTION (HR)

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Background: HR is a standard treatment option in resectable CR liver metastases patient. Very expensive multicomponent treatment has allowed raising recurrence-free survival to 6-9%.

Purpose: To evaluate the CR resectable liver metastases treatment included preoperative TACE with oxaliplatin following HR.

Material and methods: A prospective nonrandomized trial, including 66 synchronous and metachronous CR resectable liver metastases patients, has been completed. Resectability criteria: removal of all metastases, portal vein, more than 2 hepatic vein and vein cava inferior invasion absence. HR has been performed in the group 1 (n=40, average age 59 years, 25 men, 15 woman). TACE with 50-100 mg oxaliplatin following HR in 4-6 weeks has been carried out in group 2 (n=10, 58, 2/8). TACE with 30-50 mg doxorubin following HR in 4-6 weeks has been conducted in group 3 (n=16, 56, 8/8).

Results: Median and 3-year recurrence-free survival (RFS) have amounted to 13,1 months and 25,7±7,0% in group 1, 35,7 months and 58,3±16,1% in group 2, 13,8 months and 6,3±6,1% in group 3, respectively (p=0,017). RFS was higher in group 2 versus group 1 (p=0,04) and group 3 (p=0,003). Median, overall 3-and 5-years survival have amounted to 31,6 months, 46,8±8,0% and 37,1±8,0%, respectively in group 1. Median hasn't obtained, overall 3-and 5-years survival have amounted 77,1±14,4% и 51,4±17,7% in group 2. Median, overall 3-and 4-years survival have amounted 29,5 months, 41,7±12,9% и 16,7±10,5%, respectively in group 3. Statistically significant differences of overall survival haven't obtained (p=0,13).

Conclusion: Using TACE with oxaliplatin and HR in CR resectable liver metastases patients has improved recurrence-free survival. The III phase of clinical trial is planned.

Disclosure: All authors have declared no conflicts of interest.

693 THE INTERIM ANALYSIS OF AN OPEN NONRANDOMIZED PROSPECTIVE STUDY COMPARING LAPAROSCOPIC SURGERY WITH XELOX CHEMOTHERAPY AND OPEN SURGERY WITH MFOLFOX6 CHEMOTHERAPY FOR RESECTABLE COLORECTAL CANCER

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Objectives: Laparoscopic colorectomy has showed many short-term benefits compared with open surgery. However, quality of life (QOL) benefits due to laparoscopic surgery were evident only in the immediate postoperative period. This study aimed to clarify whether XELOX adjuvant chemotherapy following laparoscopic colorectomy would extend the QOL benefits for colorectal cancer patients.

Methods: Patients with resectable colon cancer and high rectal cancer coming from two urban hospitals were screened and recruited. All of the patients were asked to complete the questionnaires EORTC QLQ-C30 and QLQ-CR38. Only the patients needed adjuvant chemotherapy were kept in the study and asked to complete the QOL questionnaires 3 months and 6 months post operation. The laparoscopic surgery group accepted XELOX chemotherapy (LX). The open surgery group accepted mFOLFOX6 chemotherapy (OF). The primary endpoint was the QOL post operation. The secondary endpoint included the total hospitalization days, complications of surgery and adverse effects of chemotherapy.

Results: From DEC 2008 to DEC 2009, 46 stage II/III patients were recruited and completed adjuvant chemotherapy (25 LX, 21 OF). The two groups were balanced with respect to patients' baseline characteristics. The incidences of complications of surgery and 3/4 grade adverse effects of chemotherapy were similar between two groups. Compared OF, the shorter length of incision, decreased blood loss and faster recovery of gastrointestinal function were found in LX ($P<0.05$). The median of total hospitalization days in LX was shorter than in OF (37 days *vs.* 45 days, $P=0.009$). The compliance with QOL questionnaires was 78.3% pre operation, 78.3% at 3 months and 71.7% at 6 months post operation separately. The QOL scores preoperative were similar between two groups. 3 months post operation, the patients in LX reported higher scores of body image (BI, $P=0.004$), lower scores of symptoms in the area of the gastrointestinal tract (GI, $P=0.002$) and lower scores of weight loss (WL, $P=0.021$). The superiorities of BI and GI in LX persisted to 6 months post operation ($P=0.015$ and 0.018). Moreover, more financial difficulties were reported by patients in LX than in OF both 3 and 6 months post operation ($P<0.05$).

Conclusion: Laparoscopic colorectomy with XELOX adjuvant chemotherapy provide faster postoperative recovery and sustained better quality of life throughout treatment.

Disclosure: All authors have declared no conflicts of interest.

694 ROLE AND SIGNIFICANCE OF CIRCULAR SUTURING DEVICES IN SURGICAL TREATMENT OF RECTAL CANCER

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Aim: There are no precise recommendations for the application of concrete types of sutures and suturing materials in various location of colorectal cancer. This study aimed to optimize the using of circular suturing devices and dissection of lymph nodes in surgical treatment of colorectal cancer.

Materials and methods: Patients to be treated with sphincter-preserving operations were divided into 3 groups. 1st group included 29 (35.4%) patients with tumor, located at 10-15 cm away from the edge of anorectal line. Patients from this group were treated with anterior resection of rectum with anastomosis and standard lymph nodes dissection. 2nd group had 18 (21.9%) patients with the tumor, located at 9 cm or lower from anorectal line. These patients were treated with low anterior resection with anastomosis and extended lymph nodes dissection. The (control) 3rd group enrolled 35 (42.7%) patients with various location of the tumor in rectum. Control group patients were treated by abdominal resection of rectum with standard lymph nodes dissection (19 patients with pulling proximal parts of colon into anal canal and 16 patients with pulling sigmoid colon into anal canal). Reconstructive recovery stage was carried out as one step in 56 patients and in two steps in 26 patients.

Results: There are significance differences regarding the short term effects of these three groups, such as post-operative complications: suppuration of post-operative wound, incompetence of anastomosis, acute adhesive intestinal obstruction, bleeding, necrosis and retraction of pulling colon. Two study groups were much better than the control group. The long term effects manifesting by three year survival rate in group I, II and III were 82,8% (p=0.0084), 77.8% (p=0.091) and 65.7% respectively. Quality of Life scales are higher for group I and II than group III.

Conclusion: Low anterior resections with extended lymph nodes dissection demonstrated to be superior to abdominal resection of rectum in following indices: decrease of the local recurrences, prolongation of life duration, and improvement of physical and psychological status.

Disclosure: All authors have declared no conflicts of interest.

695 IMPACT OF ADJUVANT CHEMOTHERAPY ON SURVIVAL OF PATIENTS WITH STAGE II COLON CANCER: RETROSPECTIVE STUDY

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Background: The survival benefit of 5-FU-based adjuvant chemotherapy for stage III colon cancer patients have led some physicians to recommend adjuvant chemotherapy for their stage II colon cancer patients.

Objectives: To investigate effect of 5-FU-based adjuvant chemotherapy in stage II colon cancer patients (pts) as regards disease-free survival (DFS), overall survival (OS) and to correlate treatment outcome in relation to different clinicopathological features.

Materials and methods: Data of stage II colon cancer pts (273 pts) who received adjuvant chemotherapy in Oncology Unit of MRI, Alex. Univ. from 01/1995 to 12/2004 were including: (Age, Sex, Family history, Tumor histology, Tumor marker (CEA), Tumor grade, No. of lymph nodes dissected, Vascular invasion and Bowel obstruction). Adjuvant Chemotherapy in form of 5-FU+Ca leucovorin (Regimens as Mayo clinic or De Gramont), Doses and No., of cycles were registered.

Results: Pts presented with symptoms duration less than 6 months had better OS at 3 years. Pts received 6 cycles had better DFS. Intestinal obstruction was accompanied by lower OS at 3 and 5 ys and DFS at 3 ys. Vascular invasion had an impact on both DFS and OS at 3 and 5 ys. Higher level of CEA was accompanied by lower DFS and OS at 3 and 5 ys. Pts with poorly differentiated tumors had lower DFS. For all pts, DFS at 3 and 5 years were (72.9%) and (57.1%), while OS at 3 and5 years were (86.1%) and (73.6%) respectively.

Conclusion: No improvement in OS, But DFS was better with adjuvant chemotherapy. Pts with high risk features get benefit from adjuvant chemotherapy. Consider co-morbidities and tolerance to chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

696 CLINICAL OUTCOME OF PATIENTS TREATED WITH HEPATIC ARTERIAL INFUSION OF OXALIPLATIN AND L-FOLINIC ACID MODULATED 5-FLUOROURACIL FOR INOPERABLE COLORECTAL CANCER LIVER METASTASES, A SINGLE CENTER EXPERIENCE

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Background: Despite the progress made in the treatment of metastatic colorectal cancer (CRC), 5-year survival rates for patients (pts) with inoperable liver metastases (LM) remains poor. Encouraging anti-tumor activity has been reported with hepatic arterial infusion (HAI) of oxaliplatin (OXA) containing chemotherapy but long-term outcome of pts treated with this modality remains undetermined at present.

Methods: The clinical outcome of pts with unresectable CRC-LM treated with HAI of OXA in combination with l-folinic acid (400 mg over 2-6 h iv) modulated continuous HAI of 5-fluorouracil (ci5-FU/FA) (2400 mg/mÂ² over 42 HAI q2w) in a single center (UZ Brussel) was analyzed after a median follow up of 55 months (range 82-6).

Results: 23 Caucasian pts (17M/6F, median age 56,7 (range 28-79) at initiation of HAI) were identified. Characteristics: 11 rectum, 12 colon; 3 pts received adjuvant chemotherapy; 7 pts received oxali-HAI as 1st-line and 16 as 2nd-line chemotherapy. All except 2 hepatic artery catheters were placed during laparoscopy. A median of 7,2 (range 2-15) cycles of OXA-containing chemotherapy were administered. Cystic bile duct dilatation with arterio-biliary shunt (gr1) was observed in one pt. The most frequent treatment related adverse events of gr3 were: abdominal pain (9 pts), elevated liver enzymes (n= 5 pts), duodenal ulcer (1 pt), sensorial polyneuropathy (8 pts), and reversible toxic interstitial pneumonitis (1 pt). There were no gr4 or 5 AE's. Reasons for stopping HAI were: catheter thrombosis in 10 pts (43%), unacceptable toxicity in 5 (22%) and PD in 3 (13%). Objective response (RECIST) were: 1 CR, and 18 PR (BORR = 82%), and 4 SD. Median TTP from initiation of HAI: 7,4 mths (95% CI 6-8,9); median OS from diagnosis of stage IV disease: 39 mths (95% CI 30-47) and from the initiation of HAI: 23 mths (95% CI 12 - 35).

Conclusion: HAI of OXA plus ci5-FU/FA is feasible and results in a favorable survival of pts with unresectable CRC-LM. This experimental treatment is associated with specific but manageable toxicity. Randomized clinical trials on OXA-HAI in this population of patients seem warranted.

Disclosure: All authors have declared no conflicts of interest.

697 RANDOMIZED PHASE II STUDY OF HEPATIC ARTERIAL INFUSION WITH OR WITHOUT ANTINEOPLASTONS AS ADJUVANT THERAPY AFTER HEPATECTOMY FOR LIVER METASTASES FROM COLORECTAL CANCER

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Background: Hepatic recurrence occurs in a high rate after hepatectomy for patients with colorectal metastasis to the liver. Therefore, hepatic arterial infusion chemotherapy (HAI) has been applied as an adjuvant therapy after hepatectomy. However, HAI is less effective against extra-hepatic recurrence. Antineoplastons (AS2-1 and A10) are naturally occurring peptides and amino acid derivatives found in human blood and urine. Sodium phenylacetate is the main component of AS2-1 and A10. The small peptides reportedly control neoplastic growth and have minimum adverse effects. It seems to be reasonable to apply systemic administration of antineoplastons in addition to HAI after hepatectomy in colorectal metastasis to the liver. This randomized phase II study compares the efficacy of hepatic arterial infusion with or without antineoplastons as postoperative adjuvant therapy for colorectal metastasis to the liver.

Patients and methods: A total of 65 patients who underwent hepatectomy, thermal ablation or their combination for liver metastases from colorectal cancer enrolled between 1998 and 2004 from Kurume University hospital. The patients were randomly assigned to receive systemic antineoplastons (infusion A10 followed by peroral AS2-1) plus HAI using 5-fluorouracil (group A) or HAI alone (group B) by the number of metastases and presence of extra-hepatic metastasis at the time of or before operation. The primary endpoint was mode and extent of recurrence, and secondary endopoints were cancer-specific survival, disease-free survival, rate of re-surgical treatment and adverse effects.

Results: Thirty two patients were randomly assigned to group A and 33 to group B. The cancer-specific survival rate in the group A was higher than that in the group B. Although the disease-free survival rates were similar between the groups, the rate of single organ recurrence and re-surgical treatment was higher in the group A. In addition, the extent of recurrent tumors in the group A tended to be within re-surgical treatment. The major adverse effects of antineoplastons were fullness of the stomach and phlebitis. However, no additional toxicity such as bone marrow suppression, liver dysfunction and renal dysfunction was found in the group A.

Conclusion: Antineoplastons appears to be useful as an adjuvant therapy in addition to hepatic arterial infusion after hepatectomy in colorectal metastases to the liver.

Disclosure: All authors have declared no conflicts of interest.

698 RADIOEMBOLIZATION AND SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH HEPATIC METASTASES FROM PRIMARY COLORECTAL CANCER

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Introduction: Hepatic metastases are a dominant factor determining survival in patients with metastatic colorectal cancer. Radioembolization (RE) using Yttrium-90 labelled resin microspheres (SIR-SpheresÂ®) in combination with systemic 5-

Fluorouracil (5FU) based chemotherapy is an effective treatment for patients with hepatic metastases from colorectal cancer. This review investigated the utility of RE in patients with metastases confined to the liver.

Methods: Patients recruited in three first-line metastatic colorectal cancer studies were considered for inclusion. Patients eligible for inclusion had metastatic colorectal cancer confined to the liver. Patients received a single implantation of SIR-spheresÂ® and ongoing infusional 5FU based chemotherapy. Chemotherapy was administered until complete response, resection, disease progression or unacceptable toxicity. Response rate (RECIST), progression-free survival (PFS), overall survival (OS) and safety were reviewed.

Results: 31 patients were accrued between 1999 and November 2009. Median follow-up is 5.5 years. 16 patients received systemic 5FU chemotherapy, 15 received systemic FOLFOX chemotherapy. Best response was complete in 5 patients (16%), partial in 24 (75%) and stable in 3(9%). Median PFS was 13.2 months, median PFS in the liver was 16.4 months, median OS was 30.7 months. 7 patients remain alive with a median follow up of 4.7 years (range 0.6 to 7.7). 1 patient died of radiation induced liver disease without documented progression of disease.

Conclusions: The combination of RE and 5FU based chemotherapy appears effective in controlling liver metastases from colorectal cancer. This benefit of multi-modality therapy was reflected in the response rate, PFS and OS when compared with historical comparators. Outcomes are awaited from ongoing phase III clinical trials of radioembolization and systemic chemotherapy for patients in this disease setting. In patients with other tumour types where liver metastases are the dominant site of disease, further studies exploring the safety profile, the impact on quality of life and survival endpoints associated with RE are worthwhile.

Disclosure: M.J. Tapner: Clinical Trials Manager, Sirtex Technology Pty Ltd

P. Gibbs: Sirtex Advisory board member and have received honoraria for radioembolisation-related talks

All other authors have declared no conflicts of interest.

699 RAPID PROGRESSION OF EXTRAHEPATIC DISEASE IN SELECTED PATIENTS WITH COLORECTAL CANCER LIVER METASTASES AFTER YTTRIUM-90 RADIOEMBOLIZATION

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Introduction: Intra-arterial Yttrium-90 radioembolization is a novel treatment modality for metastatic colorectal cancer (CRC) patients with unresectable, chemorefractory, liver dominant disease. In this pilot study we assess the influence of limited extrahepatic disease on clinical outcome.

Methods: For this study all consecutive patients with CRC liver metastases, progressing upon standard systemic treatment, treated with Yttrium-90 radioembolization in our hospital in 2009, were retrospectively analyzed. Outcome parameters were response of liver lesions according to RECIST (partial response, stable or progressive disease), extrahepatic tumor response defined as early (within 3 months after treatment) change in size or number of extrahepatic lesions (stable or progressive disease) and survival. Response was evaluated using computed tomography (CT) or magnetic resonance imaging (MRI) at baseline, and at one and three months after treatment.

Results: A total of 9 patients completed treatment for this study. Six patients presented with limited extrahepatic disease (4 male, 2 female; mean age, 55 yrs; mean tumor load 17.3%; treatment, whole liver n=2, lobar in 2 tempi n=2, right lobe only n=2) and three patients had liver-only disease (1 male, 2 female; mean age, 60 yrs; mean tumor load 16.0%; treatment, whole liver n=2, right lobe only n=1). Response of liver lesions in the extrahepatic group was stable disease in 4 patients, partial response in 1 patient and 1 patient was lost to follow up. Response of liver lesions in the liver-only group was stable disease for all 3 patients. At three months follow up, progression of extrahepatic disease was observed in 5/6 patients in the extrahepatic group and 0/3 in the liver-only group. In total three patients died during follow-up, all of whom had extrahepatic lesions at baseline.

Conclusion: In this small series we observed and reported for the first time unexpected rapid tumor growth of extrahepatic lesions after Yttrium-90 radioembolization, while liver lesions responded. We hypothesize that radioembolization may induce a systemic response which triggers growth of extrahepatic lesions, such as release of angiogenic factors.

Disclosure: All authors have declared no conflicts of interest.

700 A PILOT TRIAL OF PREOPERATIVE CHEMORADIOTHERAPY USING CAPECITABINE, EXTERNAL BEAM RADIATION AND CETUXIMAB FOLLOWED BY DEFINITIVE SURGERY IN PATIENTS WITH LOCALIZED (NON-METASTATIC) RECTAL CANCER

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Purpose: To evaluate the efficacy and safety of preoperative concurrent cetuximab, capecitabine and radiotherapy in the treatment of resectable locally advanced rectal cancer (LARC).

Methods and materials: We conducted a pilot trial to assess pathological complete response, tumor downstaging, safety of cetuximab (Anti EGFR) given weekly for 7 cycles, starting with an initial dose of 400 mg /m2 one week (day -6) before radiation therapy, followed by 250 mg/m2/week on days 1,8,15,22, 29 and 36 of radiation therapy in addition to Capecitabine at a dose of 1650 mg/m2 (divided in 2 doses, q12hours), daily throughout the 5.5 week course of preoperative irradiation, starting with the first day of radiation and ending with the last day of radiation. Preoperative radiation therapy was given to a total dose of 45Gy in 25 fractions over 5 weeks using a 4-field box technique followed by a tumor bed boost of 5.4Gy in 3 fractions (1.8Gy daily fractionation) using a 3-field technique. The patient then had rest for 6-8 weeks before proceeding with surgery.

Results: From June 2008 till June 2009, a cohort of 15 patients with median age of 52 years, 10 males and 5 females were enrolled. 73.3 %had ECOG performance status of 1. 14 patients were K-RAS WILD type (retrospective analysis).Clinical staging at presentation was T3, N1, N2 disease found in100%, 80%, and 20% by endoscopic ultrasound respectively. In 26.7% the tumor was fixed. Eight patients had tumors less than or equal to 5 cm distant from the anal verge .15 patients had surgery, sphincter preservation was achieved in 11 patients (73.3%), with pathological complete remission rate of 13.3% .Tumor and nodal down staging occurred in 60%, 53.3% respectively. One patient was found to be metastatic at surgery. Grade $^{3}/_{4}$ toxicities were mainly diarrhea (20%), skin toxicities (33.3%), nausea andvomiting (13.4%).With median follow up of 13 months ,13 patients(86.6%) are relapse free.

Conclusion: The addition of cetuximab to preoperative capecitabine and radiation therapy is feasible with encouraging results; a further larger randomized trial of this combination is warranted.

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701 OPTIMAL SCHEDULE OF CONCOMITANT CHEMORADIOTHERAPY (CRT) WITH S-1

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Purpose: Preoperative concomitant CRT consisting of radiation (RT) and 5-fluorouracil-based chemotherapy improves the local control of locally advanced rectal cancer (LARC), but the optimal combination regimen is a matter of controversy. S-1, a novel oral fluoropyrimidine, has demonstrated comparable therapeutic efficacy with Uracil/tegafur (UFT) plus oral leucovorin in advanced colorectal cancer. The aim of this preclinical study was to identify the optimal sequencing to cause potent radiosensitization by S-1.

Methods: Mice bearing KM20C, human colon cancer, in the thigh were treated. The tumor growth delay (GD) after a single dose (sgl.RT) of 5 Gy (on day 1) or fractionated daily dose (fr.RT) of 2 Gy (on days 1-4) with or without S-1 given orally for 2 weeks, was assessed. Synergism of the combinations that exhibited a statistically significant difference when compared with RT alone was calculated by the following formula: Synergy ratio = (GD in combination) / [(GD by S-1) + (GD by RT)]. A result of 95% CI greater than 1 indicates a greater than additive response.

Results: A greater than additive effect of S-1 on tumor responses to sgl.RT was observed when S-1 was given before RT, but it was only additive when RT preceded S-1. When S-1 was combined with fr.RT, a statistical significant increase in GD by 3.7 days, compared with sgl.RT, was observed, although sgl.RT caused almost the same GD as fr.RT. Dose-dependent increase of GD by combination with S-1 and fr.RT was observed. With regard to radiosensitization by S-1, however, the combination of 4 mg/kg S-1 plus RT demonstrated larger synergy ratio than 8 mg/kg S-1 plus RT (1.78 vs 1.39), because larger GD was observed by 8 mg/kg S-1 alone. There was no significant difference in GDs those observed when S-1 was given from 120 before fr.RT to just after fr.RT (P=0.76) and in all time intervals, a synergistic treatment effect of S-1 on tumor responses to fr.RT was observed (Synergy ratios; 1.32-1.48). The highest synergy ratio was obtained for the schedule in which S-1 was given 40-80 min before fr.RT.

Conclusions: The broad timing of combination schedule for CRT with S-1 must be a great advantage for clinical setting. These results suggest that S-1 is a promising new candidate in combination with preoperative RT in LARC.

Disclosure: All authors have declared no conflicts of interest.

702 THE TREATMENT OF METASTATIC RECTAL CANCER (MRC): A REVIEW OF THE MULTIDISCIPLINARY APPROACH AT THE OTTAWA HOSPITAL CANCER CENTRE (TOHCC)

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Background: There is significant controversy surrounding the management of surgically resectable MRC. The use and timing of neoadjuvant chemotherapy, pelvic radiation, and relative risks and benefits of a combined surgical resection are areas of debate among surgeons, medical, and radiation oncologists. The TOHCC multidisciplinary Cancer Conferences (MCC) provide an opportunity to discuss these cases and propose treatment plans for these patients.

Methods: We conducted a retrospective chart review of all the cases of MRC which were discussed at MCC at the TOHCC from November 2007 until October 2009. Information collected included patient demographics, site of metastases, the treatment they received prior to their case being discussed at MCC, the treatment plan discussed at MCC, treatment actually administered post MCC discussion, and patient outcome at 6 months.

Results: Forty-two patients with MRC were reviewed. The most common sites of metastases were liver (45.2%) and lung (31%). Once diagnosed with metastatic disease, prior to the MCC, patients had received the following treatments alone or in combination: chemotherapy (33.3%), radiotherapy (21.4%), surgery (19.0%), no treatment (n=57.1%). After the MCC, 38 patients (90.5%) received the treatment recommended during the review, while 4 (9.5%) did not. Treatment post MCC included: chemotherapy (neoadjuvant: 38.1%; adjuvant: 23.8%; palliative: 28.6%), radiotherapy (neoadjuvant: 14.3%; adjuvant: 7.1%; palliative: 7.1%) and surgery (31.0%), 10 (23.8%) of which underwent a metastatectomy.

Conclusions: There is no standardized approach to the management of MRC. Given its complexity, many cases are reviewed at MCC, which allow coordination for multidisciplinary care of these patients. Furthermore, following discussion of their case at MCC rounds, a significant proportion of patients with metastases were treated for cure. The results of this study suggest that in a majority of cases, the recommendations brought forth are acted upon. Given that these meetings have a significant impact on the treatment plan and outcome of patients with MRC, they should represent the standard of care when treating this disease.

Disclosure: All authors have declared no conflicts of interest.

703 LONG TERM SURVIVAL IN ADVANCED RECTAL CANCER AND THE EFFECTS OF TREATMENT METHOD

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Introduction: There are around 950 000 new cases of colorectal cancer in the world each year with about 500 000 patients dying [3]. According to the Cancer–Registry of Ukraine in 2007 there were 9163 rectal cancer (RC) [1]. Treatment of RC is increasingly complex and the role of combined therapy remains a matter of debate [1, 2]. A large proportion of advanced RC (ARC) show high mortality, as the low efficiency of existing methods necessitate the search for new standards of diagnosis and treatment of RC .

Materials and methods: A retrospective analysis was made of 321 cases of ARC with stages III (Dukes-MAC C,T⊂2-4N⊂1-2M⊂0) and IV(Dukes-MAC D, T⊂allN⊂allM⊂1) treated in the Transcarpathian region in the periods 1994-1999, and 2000-2004 years by combined (Surgery+ Radiotherapy) and complex (Radiotherapy+Surgery+Chemotherapy) methods.

Results: In1994-1999 there were 158 cases of ARC, in stage III–93, in stage IV–65. In 2000-2004 years were 163 cases of ARC on stage III-118, stage IV – 45. Neoadjuvant radiotherapy in dose-25 Gy or in dose- 40-60 Gy was standard. Chemotherapy was carried out under the Mayo-regimen in most cases, but use new drugs (Xeloda, Oxaliplatin) in some cases 2000-2004. Standard surgery procedures were performed effectively the same in all periods without liver surgery. Long term results are presented in the Table1. Table1.Long term results of treatment of ARC

Abstract: 703 Table 1

Term in years	Stage , year period, treatment method(cases/%)							
	Stage III				Stage IV			
	1994-1999		2000-2004		1994-1999		2000-2004	
	combined	complex	combined	complex	combined	complex	combined	complex
1	40/80	36/83,7	42/84	62/91	22/55	15/60	18/72	19/95
3	32/64	22/51,2	36/72	55/56,1	10/25	8/32	9/36	15/75
5	18/36	14/32.5	22/44	30/44,1	1/2,5	2/8	2/8	5/25
Total 5year	93/34,4		118/44		65/4,6		45/15,5	

Conclusions: 1.Correct selection of treatment strategy and individual approach allows for the improvement of the results of 5-year survival. 2.In III stage - choice of treatment is a matter of debate. 3.In IV stage - the application of new generations of drugs in complex treatment help to achieve a 5-year survival of 25%.

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704 CIRCULATING TUMOR CELLS (CTCS) IN LOCALLY ADVANCED RECTAL CANCER (LARC) PATIENTS UNDERGOING NEOADJUVANT TREATMENT.

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Background: CTCs detected at baseline and at disease-evaluation time-point during treatment seems to be an independent prognostic factor in metastatic colorectal cancer while its role in early stages is under investigation. Nowadays no data have been published in patients affected by LARC. Aim of the study: To investigate the role of CTCs in patients with LARC undergoing neo-adjuvant chemo-radiotherapy (CT-RT) followed by curative resection. Primary end-points are evaluation of CTCs rate, correlation of CTCs at baseline with main patients characteristics, disease-free and overall survival and correlation of serial CTCs sampling with outcome.

Materials and methods: In a prospective single institution study, cT3-4 and/or N+ rectal cancer patients staged by rectal ultrasound and/or pelvic MRI and chest-abdomen CT scan, received capecitabine (825 mg/mq, orally, tid continuously) with concomitant external radiotherapy (50.4 Gy/28 fractions), followed by two cycles of capecitabine (1000-1250 mg/mq, orally, tid 14/21 days). Surgical treatment comprises low anterior resection or abdomino-perineal resection with total mesorectal excision. CTCs are evaluated at baseline (t0), after neoadjuvant therapy, before surgery (t1), within 7 days after surgery (t2), and at 6-month follow-up (t3) and are enumerated with immunomagnetic separation in 7,5 ml peripheral blood in first 18 cases and 22,5 ml for subsequent ones (CellSearch System, Veridex Inc).

Results: From July 2008 to February 2010 40 patients (25 M, 15 F; median age 63 yrs: range 44-83) underwent t0 sampling; 33 completed CT-RT and therefore underwent t1 and t2 sampling. Nowadays 19 patients have completed t3 sampling. At t0, t1 and t2 9/40 (22.5%), 4/33 (13.8%) and 1/33 (3%) patients respectively presented at least 1 CTC (p=0.07 t0 vs t2, Mc Nemar p value). Among the 19 patients who underwent t3 sampling no CTCs were detected. The median of CTC detected was 1 CTC for t0 as well as for t1 and t2.

Conclusions: CTCs ≥ 1 are present in 22% of our population texted at baseline. It seems that neoadjuvant CT-RT followed by radical surgery has an impact on CTCs reduction. However, these assumptions need to be confirmed by further data. Recruitment is ongoing.

Disclosure: All authors have declared no conflicts of interest.

705 LOCAL RECURRENCE OF RECTAL CANCER IN A DEVELOPING COUNTRY: HOW TO MANAGE?

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Background: Several questions arise in the management of local recurrence of rectal cancer. + How to select patients who may benefit from reoperation? + When neoadjuvant treatment is still possible, is it useful to give preoperative radiation or

chemoradiation? + What can we expect from excision of recurrences in terms of survival and quality of life?

Materials and methods: We conducted a retrospective study over 9 years (2000 - 2009) of 113 rectal cancer.

Results: 14 cases of local recurrence were found, i.e. 12.4%. The location of the initial primary tumor was the rectum, respectively, in peritoneal, 10 cases (70%); the middle rectum, 6 cases (42%); the lower rectum in 4 cases (28%); and in 4 cases level or upper rectum (28%) Recurrence occurred within an average of 21.4 months, with a median ranged from 6 months - 5 years (50% in the first year, 64% 2 years, 12 of RLR were clinically symptomatic (86%). Confirmation of diagnosis was based on rectoscopy + biopsy because of suspected lesion on CT scan or high level on ACE (9 cases: 64%). A neoadjuvant treatment of RCC was made in two cases. Surgical management was performed on all cases. Only three patients had a curative resection.

Conclusion: The occurrence of RLR is fraught with consequence, the selection of patients for surgery with curative intent is crucial in its management. Prevention must be central in the initial management of rectal cancer. Practices must be better defined to provide quality removal optimum and reduce the incidence of RLCR.

Disclosure: All authors have declared no conflicts of interest.

706 DECODING OF COLON CANCER AND BREAST CANCER ASSOCIATION

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Purpose: Previous reports in the literature suggested that breast cancer could play an important role in colon cancer development. To investigate this controversial association, we analyzed the characteristics of patients presenting these two cancers. We also looked upon the combined effects of these tumours on patient survival and outcome.

Patients and methods: We collected cases of women who were treated for breast and colon cancer at Rene Huguenin Center between January 1972 and December 2008. We identified 19 patients who presented these two malignancies. Statistical tests were two tailed and were performed using SPSS statistical software.

Results: Median age was 66 years old. Among the 19 patients, 6 women had a familiar history of cancer and underwent genetic counseling. Both cancers had occurred metachronously in 21% of patients. Breast cancer was diagnosed first in 57% of women. The median time interval between the two cancers diagnosis was 34 months. For patients who presented the association, they had smaller TNM stage at diagnosis of colon cancer than those with colon cancer alone. We described the histology features, the modality of treatment, outcomes and time to progression. Colon cancer patients associated with breast cancer experienced 21 % of local or metastatic relapses while the other colon cancer patient treated at the centre with no other malignancy had a higher rate of relapse of 27.7%. Multivariate tests of the relationship between association and outcome were performed with Cox proportional hazards analysis. Several germline mutations may account for both colon and breast cancer (Peutz Jeghers syndrome, BRCA). In contrast, cancer is infrequent in Hereditary Non Polyposis Colorectal Cancer (HNPCC).

Conclusion: Colon cancer outcome seems to benefit from continued follow up for breast cancer. Genome-wide association studies may help to identify susceptibility genes for both breast and colon cancer. However, environmental factors like reproductive factors, exogenous female hormone use or diet, may also account for association of breast and colon cancer. This association deserves further studies.

Disclosure: All authors have declared no conflicts of interest.

707 SLEEP DISRUPTION IN COLORECTAL CANCER PATIENTS

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The aim of this study was to examine the prevalence of insomnia in colorectal cancer (cc) patients

Patients and methods: In this study were entered 48 (30 male and 18 female) cc patients, mean age 56 years, receiving chemotherapy and reporting sleep difficulties.

Results: During chemotherapy, 35,4% of the cc patients reported insomnia symptoms, and 43,75% met the diagnostic criteria for insomnia syndrome. CC patients younger than 56 years were significantly more likely to experience either symptoms of insomnia or insomnia syndrome (p=0,0001). 58,3% of the cc patients reported that their insomnia symptoms remained unchanged during chemotherapy. Patients with insomnia complaints had significantly more depression and fatigue than good sleepers ($p < 0,0002$).

Conclusion: 35,4% of the cc patients reported symptoms of insomnia and 43,7% met diagnostic criteria for insomnia syndrome. Insomnia is a prevalent severe problem among cc patients during chemotherapy and it must be treated.

Disclosure: All authors have declared no conflicts of interest.

708 OUTCOME OF BRAIN METASTASES FROM COLORECTAL CANCER; A SINGLE INSTITUTE EXPERIENCE

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Background: The evolution of new chemotherapeutic agents has prolonged survival of patients with metastatic colorectal cancer and showed an increased incidence of uncommon metastatic sites like brain. The aim of this study was to evaluate trends of presentation and the efficacy of different treatment strategies in management of this rare metastatic site.

Methods: Patients with brain metastases from colorectal cancer treated in our Institute of Oncology between January 2000- June 2009 were identified. The baseline demographic and histopathological characteristics were evaluated retrospectively. All patients had solid brain metastases without leptomeningeal carcinomatosis.

Results: A total of 14 patients (8 male, 6 female) with median age of 60 years (range: 43-72 years old) were identified. Median follow-up time was 28 months. 64 % had extracranial metastasis at time of diagnosis. The most common site of metastases at presentation was liver (28.4 %) followed by bone (14 %) and lung (7%) . Primary site of tumor was sigmoid colon (57 %), rectum (28 %) and cecum (14 %). Primary tumor tended to be in more advanced stage (T4: 50%, T3: 28 %, Tx: 22%). Only one patient presented with brain metastases as first site of progression without any extracranial metastases. The most common site of metachronous extracranial metastases was lung (49 %), 8 patients had solitary metastases while the rest were multiple. Nine patients had undergone surgery for brain metastases and followed by whole brain radiotherapy. Five patients were treated with radiotherapy without surgery due to multiple metastases. Two patients in surgery group and two patients in radiotherapy only group received chemotherapy (mainly irinotecan based) after detection of brain metastasis. The median time interval between first cancer diagnosis and brain metastasis was 26 months and mean overall survival (OS) rate for the whole patient group was 54 months. The mean OS rate for patients in surgery group was 62 months and 36 months for the rest of the patients ($p>0.05$).

Conclusions: Despite the recent developments in systemic treatment of metastatic colorectal cancer, survival after brain metastasis has not improved much over time. High rates of extracranial disease and small number of patients receiving systemic therapy after brain metastases limits the development of new strategies. In our study, although not statistically significant, there was a trend towards better survival rate for patients who had undergone surgery for brain metastases. However better systemic control of extracranial metastases still remains to be the cornerstone of management with brain metastases.

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