Our data suggests that the poor outcomes reported for diabetic patients in other studies are potentially explained by multiple factors that bias for poor tumour related outcome and overall survival. The inferior survival for diabetics with stage I CRC is likely due to death from non-cancer related causes, possibly cardiovascular complications. Follow up data examining disease free survival for stage III CRC for each group will determine if inferior outcomes in diabetics is due to increased cancer relapses, perhaps related to less well differentiated tumours.

3053 POSTER

Phase II study of combination with irinotecan and S-1 (IRIS) for inoperable recurrent advanced colorectal cancer (HGCSG0302). Safety analysis

S. Yuki[1], Y. Komatsu[1], N. Machida[1], M. Ozasa[1], K. Nishi[2], T. Miyagishima[2], T. Kato[2], M. Nakamura[2], M. Asaka[1], Y. Sakata[3]. *[1]Hokkaido University Graduate School of Medicine, Gastroenterology, Sapporo, Japan; [2]Hokkaido Gastrointestinal Cancer Study Group, Gastroenterology, Sapporo, Japan; [3]Misawa city hospital, Medical Oncology, Misawa, Japan*

Background: We planned to conduct a phase II study of combination with irinotecan and S-1, a new oral anticancer drug of the fluorinated pyrimidine type. We reported the interim reports of this study in colorectal cancer patients at ASCO 2006.
Methods: The antitumor effect was the primary endpoint, while the safety, progression-free survival time, and median survival time were the secondary endpoints. The subjects were untreated patients with inoperable advanced colorectal cancer aged 20−75 years. Irinotecan was administered at a dose of 100 mg/m^2 (on days 1 and 15) as an intravenous infusion over 90 minutes, and oral S-1 (40 mg/m^2) was administered after breakfast and dinner and then withdrawn for 2 weeks.
Results: Forty patients were enrolled in the present study. There were 23 men and 17 women. The median age was 62 years (range: 34 to 74 years). Two patients showed grade 4 neutropenia, but the next course could be given safely after dose reduction. Three patients had grade 3 diarrhea, but therapy could be continued with addition of an antidiarrhea drug. No other serious adverse reactions occurred (either hematological or non-hematological), and all patients could receive therapy safely on an outpatient basis. Forty pts. are evaluable for efficacy: RR was 52.5% (CR 1, PR 20, SD 17, PD 2, 95% CI, 37−68%) and Disease Control Rate (CR+PR+SD) was seen in 96.0% of pts. PFS of this regimen is 311 days. MST is not reached.
Conclusions: IRIS therapy achieved a high response rate and could be given safely. These findings suggest that the therapy has potential as first-line treatment for inoperable advanced recurrent colorectal cancer. It seems that IRIS is a good treatment equal to FOLFIRI. Non-inferiority randomized Phase III trial of IRIS vs. mFOLFOX6 (IFOX study) was planned, and it has been already started now. The latest data will be reported at the meeting.

3054 POSTER

Comparison of paired patient primary and liver metastatic colorectal cancer (CRC) tissues for epidermal growth factor receptor (EGFR) protein expression and the presence of mutations in the EGFR tyrosine kinase domain

J.A. Maroun[1], D.J. Jonker[1], H.C. Birnboim[1], T. Moyana[2], D. Wang[2], D. Samson[1], I. Gorn[1], I. Teo[2], G. Chiritescu[1], H. Marginean[1]. *[1]The Ottawa Hospital Regional Cancer Centre, Medical Oncology, Ottawa, Canada; [2]The Ottawa Hospital, Anatomical Pathology, Ottawa, Canada*

Background: Previous studies indicate that drugs that target the EGFR signaling pathways can induce objective responses, prolong time to progression and improve survival for CRC patients with EGFR expression in their primary tumour. However EGFR expression in the primary tumour may not predict response in the metastatic location, and little information is available about the correlation of EGFR expression between the primary tumour and the metastatic site. In other tumour sites, the presence of EGFR mutations was associated with efficacy in a subset of patients.
Objectives: The goal of this study is to correlate EGFR expression (using immunohistochemistry, IHC) between primary and liver metastatic sites of the tumour and to assess the mutational status in the EGFR kinase domain. We anticipate that high levels of EGFR will be expressed in metastatic lesions when compared to the primary tumor.
Methods: This is a retrospective study of all patients at TOHRCC who underwent surgical resection for CRC between 1999 and 2005, for whom paired paraffin-embedded tissue blocks of primary tumour and resected liver metastases were available. Seventy-four paired samples were identified. EGFR immunostaining was performed using the DakoCytomation EGFR pharmDx kit (DAKO) following manufacturer guidelines at the Department of Pathology, Faculty of Medicine, University of Ottawa. Two pathologists independently evaluated EGFR staining. To evaluate EGFR mutations, DNA was extracted and PCR was performed targeting exons 18, 19 and 21 encompassing most of the tyrosine kinase domain. PCR products were sequenced bi-directionally at the Sequencing Facility of the Ottawa Health Research Institute.
Results: EGFR staining and kinase domain sequencing has been completed on 25 paired samples. Analyses are ongoing and the study will be completed by the end of May 2007.
Conclusions: Final results will be presented at the meeting, and correlation between EGFR expression in primary tumour and metastasis will be evaluated.
Support: Funding provided by Bristol-Myers-Squibb and the Ottawa Regional Cancer Foundation

3055 POSTER

Cetuximab plus irinotecan in patients (pts) with metastatic colorectal cancer (mCRC) progressing on or after prior irinotecan therapy: final results of the LABEL study

C. de Cerqueira Mathias[1], F. Perazzo[2], S. Simon[3], L. Fein[4], J. Hidalgo[5], A.M. Murad[6], G. Lerzo[7], R. Esser[8], S. Scheid[9], A.C. Buzaid[10]. *[1]Nucleo de Oncologia da Bahia, Oncology Department, Salvador, Brazil; [2]CEMIC – Suc.Saavedra, Oncology Department, Buenos Aires, Argentina; [3]Hospital Israelita Albert Einstein, Oncology Department, São Paulo, Brazil; [4]Centro Oncologico Rosario, Oncology Department, Santa Fe, Argentina; [5]COIR – Centro Oncologico de Integracion Regional, Oncology Department, Mendoza, Argentina; [6]Hospital Vera Cruz, Oncology Department, Belo Horizonte, Brazil; [7]CODE – Clinica de Oncologia de Excelencia, Oncology Department, Buenos Aires, Argentina; [8]Merck KGaA, R& D Global Medical Affairs Oncology, Darmstadt, Germany; [9]Merck KGaA, Biostatistics and Data Sciences, Darmstadt, Germany; [10]Hospital Sirio-Libanes, Oncology Department, São Paulo, Brazil*

Background: Cetuximab (Erbitux®), an IgG1 monoclonal antibody directed against the epidermal growth factor receptor (EGFR), is active in combination with irinotecan in pts with mCRC progressing during or after prior irinotecan therapy. The European MABEL study investigated cetuximab in combination with irinotecan in 1147 heavily pre-treated mCRC pts, and found a 12-week progression-free survival (PFS) rate of 61%, median overall survival (OS) of 9.2 months and a predictable and acceptable safety profile.
Methods: This open, single-arm, phase II, 14 center study investigated this combination in pts with EGFR-expressing mCRC progressing on or within 3 months of at least 6 weeks (wks) of irinotecan-based chemotherapy. The primary objective was to assess the best overall confirmed response rate (RR). Secondary objectives included duration of response (DOR), progression-free survival (PFS), 6-weekly PFS rates, overall survival (OS), 3-monthly survival rates, and safety. Pts received cetuximab (initial dose 400 mg/m^2, then 250 mg/m^2 wkly), plus irinotecan at the same dose and schedule as pre-study (100 or 125 mg/m^2 wkly for 4/6 weeks; 100 or 125 mg/m^2 wkly for 2/3 wks; 180 or 210 mg/m^2 every 2 wks; 300 or 350 mg/m^2 every 3 wks).

Efficacy results

	All ITT patients (n = 79)
Overall confirmed RR, % [95% CI]	26.6 [17.3, 37.7]
Median DOR, wks [95% CI]	23.9 [17.1, 30.0]
Median PFS time, wks [95% CI]	17.4 [11.7, 18.9]
PFS rate, % [95% CI]	
6 wks	78 [69, 87]
12 wks	57 [46, 68]
18 wks	42 [31, 53]
24 wks	27 [17, 37]
Median OS, months [95% CI]	9.2 [7.9, 10.8]
Survival rate, % [95% CI]	
3 months	88 [81, 96]
6 months	65 [55, 76]
9 months	54 [43, 65]

Preliminary results: 71% (109/153, 2 pts missing) pts screened and in the database were EGFR-expressing. 79 pts were treated on-study: 40 (51%) male; median age 59 years [range, 27−82]; 70 (89%) with KPS $\geqslant$ 90. 19 (24%) pts had received $\geqslant$3 prior treatment regimens. 66 (84%) pts progressed within 30 days of their last course of pre-study irinotecan. Efficacy results are shown below. The most common grade 3/4 adverse

events included: diarrhea, 20%; neutropenia, 11%; acne-like rash (grade 3 only), 9%. No grade 3/4 infusion-related reactions (IRRs) were reported.
Conclusions: The overall confirmed RR of 27% observed in this heavily pretreated population fully met the expectations for the primary endpoint of this study. LABEL confirmed the activity and safety of cetuximab plus irinotecan seen in previous studies.

3056 POSTER

XPA, XPD, ERCC1 and XPG/ERCC5 single nucleotide polymorphisme (SNPs) in oxaliplatin-treated colorectal cancer (CRC)

I. Moreno-Solorzano[1], M. Monzo-Planella[2], R. Ibeas-Rollan[1], A. Navarro[2], R. Artells[2], B. Gel-Moreno[2], J. Moreno-Solorzano[3], R. Hernandez-Borlan[3], O. Etxaniz[1], J. Tello[1]. *[1]Hospital Municipal de Badalona, Oncology, Badalona (Barcelona), Spain; [2]University of Barcelona, Human Anatomy, Barcelona, Spain; [3]Hospital Municipal de Badalona, Surgery, Badalona (Barcelona), Spain*

Background: Oxaliplatin damages DNA, leading to apoptosis. XPA, XPD, ERCC1 and XPG/ERCC5 are involved in DNA repair, and polymorphic variant in these genes can influence the efficacy of oxaliplatin. We analysed SNPs in these genes and correlated the results with toxicity, time to progression and overall survival and response to oxaliplatin in advanced CRC.
Methods: 42 CRC patients (pts) recruited between April 2002 and May 2005 were treated with oxaliplatin as first line chemotherapy combined with fluoropyrimidine [Moreno I et al. Ann Oncol 2006; 17(Suppl 6): 75 (P-178)]. Update march 2007. DNA was obtained from peripheral blood cells at baseline, and allelic discrimination assay with ABI Prism 7700 was used to analyze SNPs at XPA 5′utr A/G, XPD Lys751 Gln, ERCC1 Thr/Lys and XPG/ERCC5 C/T
Results: Patients characteristics: 21 males/21 females, median age 66 yr (range, 44−79), PS 0−2. Pts with XPA genotype A/A showed lower emesis toxicity (12%) than those with A/G and G/G (20%) ($p = 0.010$). Pts with XPG C/C shower better objective response (74%), than those with C/T and T/T (35%) ($p = 0.03$). Pts with XPG C/C achieved longer time to progression (15.8 months) than those with C/T and T/T (7.5 moths) ($p = 0.009$). Pts with XPG C/C achieved better median survival (33 moths) than those with C/T and T/T (13.9 months) ($p = 0.000$). Pts with XPG C/C and XPA A/G or G/G achieved better time to progression and median survival (21.8 moths and 43.3 moths, respectively) than those others patients (7.5 months and 15.5 months, respectively) ($p = 0.000$). Cox multivariate analysis showed that gender (male), PS (<2), and genotypes XPG C/C and XPA A/G or G/G, were favourable predictive factors.
Conclusion: XPG C/C may be a predictive marker of response and genetic profile XPG C/C and XPA A/G or G/G may be a predictive marker of time to progression and overall survival in oxaliplatin CRC pts. Studies with a larger number of patients should be carried out to confirm these results.

3057 POSTER

Neoadjuvant chemoradiation for locally advanced rectal cancer. Analysis of clinical outcomes

A. Tamburini[1], S. Di Palo[1], E. Orsenigo[1], M. Ronzoni[2], C. Staudacher[1]. *[1]University Vita-Salute San Raffaele, Gastrointestinal Surgery, Milan, Italy; [2]University Vita-Salute San Raffaele, Department of Oncology, Milan, Italy*

Background: During the past few decades, significant progress has been achieved in the management of rectal cancer with the introduction of total mesorectal excision.Preoperative radiotherapy appears more effective in terms of local control and toxicity compared to postoperative therapy. Several recent studies show that 5-FU-based chemotherapy enhances tumour response to radiotherapy and preoperative chemoradiotherapy is being increasingly used for stage II and III disease.
Our prospective cohort study will evaluate the impact of neoadjuvant radiochemotherapy at first on toxicity, surgical morbidity and pCR rate and then the local and distant recurrence rates.
Patients and Methods: From 1998 to 2006, 188 consecutive patients, with a tumour with an average distance from the anal verge of 6.5 cm, were treated with neoadjuvant radiochemotherapy. 89 of them (47.4%) had the tumour localized in lower rectum, 82 (43.6%) in the middle one and 17 (9%) to the upper rectum. All the patients were studied by EUS, MR and CT to establish the clinical stage and so decide the therapeutical strategy. These patients, staged as II and III, were submitted to a “long-course” radiochemotherapy. After 4−6 weeks from the end of the neoadjuvant therapy, all the patients were submitted once again to EUS and MR and then operated on.
Results: 164 patients showed a clinical stage III and 24 a clinical stage II. No major complications related to therapy were observed and all the patients have completed the course of therapy. A complete or partial response was observed in 70.7% of the patients and pCR was found in 13.8%. We observed a significant clinical down-staging ($p < .004$). Surgical procedures (112/188 [60%] laparoscopic) carried out were: 156 AR (83.9%), 24 APR (12.9%) and 4 TEM (2.2%). We observer clinical anastomotic leak in 6.3%. Mean nodal-sampling was 14.9. Concerning yTNM, 26/188 patients (13.8%) were in stage 0, 42/188 (22.3%) in stage I, 66/188 (35.2%) in stage II and 54/188 (28.7%) in stage III. Five-years overall-survival and disease-free-survival were respectively 73% and 60%. Pre-treatment clinical stage had no prognostic significance ($p = 0.9321$). On the contrary, postoperative yTNM was significant ($p = 0.0090$) for yT ($p < 0.001$) and yN ($p < .00024$). Non-responder patients had the worse prognosis (5-years survival 30%). The variable with higher prognostic significance was yN ($p < .0003$), especially if we distinguish N1 by N2 ($p < .00022$). With a mean follow-up of 36 months, local recurrence rate was 5.7%.
Conclusions: Our data showed that neoadjuvant chemotherapy in well tolerated and don’t improve the postoperative complication. The post operative stage play an important independent prognostic role in disease free and overall survival. Future neoadjuvat trials should evaluate, with modern molecular biology techniques, correlation between reresistence markers or other molecular markers to stratify patients besed on molecular markers instead of on biologic tumours response.

3058 POSTER

Administration of reduced glutathione in FOLFOX4 regimen in advanced colorectal cancer: effect on oxaliplatin pharmacokinetics and on Pt-DNA adducts formation

M. Airoldi[1], P. Milla[2], L. Cattel[2], I. Gozzelino[2], A. Drescher[3], U. Jaehde[3], L. Branciforte[4], F. Pedani[1]. *[1]S. Giovanni Antica Sede Hospital, Medical Oncology, Torino, Italy; [2]University of Torino, Drug Science and Techn. Dept., Torino, Italy; [3]University of Bonn, Clinical Pharmacy Dept., Bonn, Germany; [4]Molinette Hospital, “Baldi e Riberi” Laboratories, Torino, Italy*

Background: Neurotoxicity is the most common oxaliplatin (OXA) toxicity in FOLFOX4 regimen for patients with advanced colorectal cancer. Recently, Cascinu et al. (JCO 2002; 20: 3478–3483) provided evidence that reduced glutathione (GSH) reduces the OXA-induced neurotoxicity, but GSH influence on the formation of Pt-DNA adducts still remains unknown. This study evaluated the effect of GSH addition on OXA pharmacokinetics(pk) and on Pt-DNA adducts formation
Materials and Methods: 28 patients were given twelve FOLFOX4 courses and randomized to receive either GSH 1,500 mg/m^2 ornormal saline solution (placebo) before OXA. OXA pk and Pt-DNA adducts formation were evaluated at cycles 5, 9 and 12. Total and ultrafiltered platinum were analyzed by atomic adsorption, Pt-DNA adducts in leukocytes (as model for tumour tissue) by adsorptive stripping voltammetry. Pk analysis were done by non-compartmental analysis, statistical analysis by non-parametric Mann-Whitney test
Results: Median total and ultrafiltered platinum pk parameters were comparable to previously reported ones, only median total AUC_{tot} show statistically significant difference being higher in the placebo arm. On the other side, ultrafiltered platinum pk parameters show no statistically significant differences The formation of Pt-DNA adducts was more pronounced in GSH arm (median value at the end of infusion 4.52 Pt atoms/10^6 nucleotides vs. 4.25 Pt atoms/10^6 nucleotides), though not statistically significant.

	Total Pt			Ultrafiltered Pt		
	GSH-OXA	Placebo-OXA	p	GSH-OXA	Placebo-OXA	p
C_{max} (mg/l)	2.47	2.66	0.855	0.196	0.197	0.882
AUC_{tot} (mg*h/l)	127.5	166.9	0.036	4.49	4.43	0.982
Cl_{tot} (l/h)	1.08	0.97	0.385	31.1	33.2	0.235

Conclusions: The addition of GSH to FOLFOX4 regimen is able to reduce the OXA-induced neurotoxicity, without affecting either the OXA pk behaviour or the formation of Pt-DNA adducts, thus assuring that the well-known clinical efficacy is unmodified.

3059 POSTER

Prospective comparison of laparoscopic vs. open total mesorectal excision (TME) for rectal adenocarcinoma

A. Tamburini, S. Di Palo, E. Orsenigo, A. Vignali, C. Staudacher. *University Vita-Salute San Raffaele, Gastrointetinal Surgery, Milan, Italy*

Background: The continue advancing of laparoscopic surgery has become possible to extend the mini invasive technique to Total Mesorectal Excision