289 POSTER

Phase II study of cetuximab combined with FOLFIRI (bi-weekly irinotecan plus infusional 5-FU and folinic acid (FA)) in patients (pts) with metastatic, Epidermal Growth Factor Receptor (EGFR)- expressing colorectal cancer (CRC)

J.L. Raoul[1], J.L. Van Laethem[2], E. Mitry[3], C. Brezault[4], F. Husseini[5], L. Cals[6], M. Peeters[7], J.C. Vedovato[8], M. Mueser[8], P. Rougier[3]. [1] *CRLC Eugéne Marquis, Département d'Oncologie Digestive, Rennes, France;* [2] *Hôpital Erasme, Bruxelles, Belgium;* [3] *Hôpital Ambroise Paré, Boulogne, France;* [4] *Hôpital Cochin, Paris, France;* [5] *Hôpital Pasteur, Colmar, France;* [6] *Hôpital Font Pré, Toulon, France;* [7] *Universitair Ziekenhuis, Gent, Belgium;* [8] *MERCK KGaA, Darmstadt, Germany*

Cetuximab (Erbitux) is a chimeric monoclonal antibody targeted against the EGFR with activity in CRC.

Objectives: This phase II trial evaluates the safety and the efficacy of cetuximab combined with a FOLFIRI regimen as first-line treatment for pts with metastatic EGFR-expressing CRC.

Methods: The initial dose of cetuximab was 400 mg/m^2, then 250 mg/m^2 i.v. weekly thereafter. FOLFIRI was administered every 2 weeks: Irinotecan 180 mg/m^2, FA 400 mg/m^2 and 5-FU 300 mg/m^2 bolus plus infusion 2,000 mg/m^2/46h in the low dose (LD) group or 400 mg/m^2 bolus plus infusion 2,400 mg/m^2/46h in the high dose (HD) group. Dose limiting toxicity (DLT) was defined as neutropenia/leukopenia, thrombopenia, alk. phosphatase, bilirubin, ASAT, ALAT or skin toxicity > grade 3; neutropenia with fever/infection, anemia, diarrhea, mucositis, creatinine, or any treatment-related organ toxicity > grade 2 during the first 3 cycles.

Results: 28/33 pts screened (85%) had EGFR expressing tumors. Of these 28 pts, 23 (15 males, 8 females) were enrolled, 10 in the LD group and 13 in the HD group. Median age was 65.4 years (35.9-75.5) and Karnofsky performance status 90 (70-100). All pts were evaluable for DLT. The LD group experienced no DLT, while 3 DLTs occurred in the HD group (diarrhea grade 3, allergy grade 3, neutropenia grade 4). Chemotherapy dose modifications were required in 1/13 pts in the HD group. Almost every pt experienced typical cetuximab-related skin toxicity, mostly of grade 1/2. At abstract submission, 21 pts on 22 were evaluable for efficacy: confirmed PR 9 (43%, C.I., 24-63%), SD 11 (52%), PD 1 (5%). Median TTP was 183 days. 7 out of these 23 patients have been discontinued from the trial for surgery of remaining metastases.

Conclusion: The combination of cetuximab with FOLFIRI is safe, feasible and easy to administer to pts with EGFR-expressing metastatic CRC and is clearly active. Additional patients are currently under recruitment (19 new patients have already been recruited) and will be treated in the HD group before considering a phase-III trial.

290 POSTER

Nordic 5-fluorouracil/folinic acid bolus schedule combined with oxaliplatin (FLOX) as first-line treatment to metastatic colorectal cancer.

H. Sørbye[1], B. Glimelius[2,3], Å. Berglund[2], T. Fokstuen[3], K.M. Tveit[4], M. Braedengen[5], D. Øgreid[6], O. Dahl[1]. [1] *Haukeland University Hospital, Department of Oncology, Bergen, Norway;* [2] *Uppsala University Hospital, Department of Oncology, Uppsala, Sweden;* [3] *Karolinska Hospital, Radiumhemmet, Stockholm, Sweden;* [4] *Ullevål University Hospital, Department of Oncology, Oslo, Norway;* [5] *The Norwegian Radium Hospital, Oslo, Norway;* [6] *Rogaland Central Hospital, Department of Hemato-Oncology, Stavanger, Norway*

Background: This Nordic multicentre phase II study evaluated the efficacy and safety of oxaliplatin combined with the Nordic bolus schedule of 5-fluorouracil (5-FU) and folinic acid (FA) (FLOX) as first-line treatment in metastatic colorectal cancer. Few studies have reported the use of a pure bolus schedule of 5FU and FA combined with oxaliplatin.

Material and methods: Eighty-five patients had measurable metastatic disease and a WHO performance status of 0-2 (58% WHO 1-2). They were treated with oxaliplatin 85 mg/m^2 as a 2-hour infusion day 1, followed by a 5-min bolus infusion with 5FU 500 mg/m^2 and 30 min later a 5-min bolus infusion with FA 60 mg/m^2. The same dose 5FU and FA were given day 1 and 2, every 2 weeks. Evaluation was done after every 4th course. The primary endpoint was the objective response rate.

Results: Fifty-one out of 79 eligible patients achieved a complete (n= 5) or partial (n= 47) response, leading to an overall response rate of 65% (95% CI 53-73%). Nineteen patients showed stable disease and 9 patients had progressive disease. The estimated median time to progression and survival were 6.9 months and 16.1 months in the intention to treat population. Nine patients (11%) received secondary surgery or radiofrequency ablation with a curative intent. A total of 762 cycles of chemotherapy were given. Neutropenia was the main adverse avent with grade 3-4 toxicity in 45% of patients. Febrile neutropenia developed in only 7 patients. No treatment related deaths were seen. Non-haematological toxicity consisted mainly of neuropathy: grade III was seen in 11 patients, grade II in 27 patients.

Conclusion: Oxaliplatin combined with the bolus Nordic schedule of 5FU/FA (FLOX) is a well-tolerated, effective and feasible bolus schedule as first-line treatment of metastatic colorectal cancer with similar response rate and survival as obtained by more complex schedules.

291 POSTER

Prospective multi-centre audit of acute complications following short course preoperative radiotherapy

A. Hartley[1], S. Giridharan[2], B. Vakkalanka[3], M.S. Anwar[4], C. McConkey[5], J.I. Geh[1], M. Churn[2], F. Adab[3], R. Grieve[4]. [1] *Queen Elizabeth Hospital, Cancer Centre, Birmingham;* [2] *New Cross Hospital, Deansley Centre, Woverhampton;* [3] *North Staffordshire Royal Infirmary, Radiotherapy Department, Newcastle-under-Lyme;* [4] *Walsgrave Hospital, Oncology Centre, Coventry;* [5] *Cancer Research UK Institute of Cancer Studies, Clinical Trials Unit, Birmingham, United Kingdom*

Introduction: Retrospective data has suggested that the risk of early complications following short course preoperative radiotherapy (SCPRT) and total mesorectal excision (TME) for operable rectal adenocarcinoma is related to patient age, radiotherapy field length and time from the first day of radiotherapy to surgery (overall treatment time (OTT)). The aim of this study was to examine these relationships in a prospective multi-centre audit.

Method: Data including patient age, radiotherapy field length, overall treatment time, surgical outcomes and complications occurring within 3 months of the 1st day of radiotherapy were collected on 107 patients treated at four radiotherapy centres between 1st October 2001 and 31st September 2002. These were compared and combined with the previously studied cohort of 176 patients treated at one centre between 1st January 1998 and 31st December 1999.

Results: In the prospective cohort (n=107) only age (p=0.001) was significantly associated with acute complications. However, both the OTT (median 9.0 vs 11.0 days p<0.0001) and field length (median 16.6 vs 17.0 cm p=0.03) were significantly shorter in this cohort. In patients from both studies (n=283) increasing age (p=0.001) and field length (independent of operation type) (p=0.02) were associated with an increased risk of acute complications.

Conclusions: Patient selection and radiotherapy technique remain important in minimising acute complications following SCPRT. Data from the Dutch TME trial suggesting an increase in 180-day mortality with increasing OTT in addition to retrospective data may be responsible for the shorter interval between radiotherapy and surgery seen in this prospective study.

292 POSTER

Tegafox, a new combination of UFT/LV and oxaliplatin as first line treatment for patients (pts) with non resectable metastatic colorectal cancer (CRC): results of a completed multicenter phase II.

J. Bennouna[1], H. Perrier, B. Paillot, J.H. Priou, J.H. Jacob, M. Hebbar, S. Bordenave, J.F. Seitz, D. Tonelli, J.Y. Douillard. [1] *Centre René Gauducheau, Service d'Oncologie Médicale, Nantes;* [2] *Hôpital Saint Joseph, Service de Gastroentérologie, Marseille;* [3] *CHU Charles Nicolle, Service d'Oncologie Médicale, Rouen;* [4] *Centre Hospitalier départemental, Service d'Oncologie Médicale, La Roche Sur Yon;* [5] *Centre François Baclesse, Service d'Oncologie Médicale, Caen;* [6] *Hôpital Calude Huriez, Service de Médecine Interne, Lille;* [7] *CHU Hôtel Dieu, Service d'Oncologie Médicale, Nantes;* [8] *Hôpital La Timone, Service d'Oncologie Médicale, Marseille;* [9] *Bristol-Myers Squibb, Département Oncologie, Rueil-Malmaison;* [10] *Centre René Gauducheau, Service d'Oncologie Médicale, Nantes, France*

Rationale design: The phase I dose escalation study of UFT®/LV in combination with oxaliplatin [ASCO 2001, Abstract no. 572] established UFT® 300 mg/m2/day d1-14, LV 90 mg/day d1-14 and oxaliplatin 130 mg/m2/day d1 every 3 weeks as the recommended phase II doses in first line non operable metastatic CRC pts. Between February 2002 and July 2002, 64 pts with bidimensionally measurable non operable metastatic CRC were enrolled in this phase II study testing this regimen as first line treatment.

Objectives: To evaluate the efficacy (Objective Response Rate) and the safety of this regimen.

Results: *Patients characteristics*: 64 pts treated; median age: 68 years (range: 38-81); ECOG PS 0,1: 63%, 37%; 36 males; tumor sites: colon 60%, rectum 23%, junction: 17%; liver metastasis 80%; prior treatment: surgery 94%, (neo) adjuvant chemotherapy: 27%, radiotherapy: 14%. *Safety:* A total of 347 cycles (median: 6; range: 1-14) were given. To date, safety has been evaluated in 47 pts. Adverse reactions per patient were G3 diarrhea: 15%; G3 nausea/vomiting: 9%; G2 sensory neuropathy: 26%; neutropenia: 8%. *Efficacy:* Objective Responses were reviewed by an independent panel of expert radiologists on the 64 patients included. One patient was non evaluable for response, 5 patients did not undergo tumor assessment for early withdrawal from the study. Among the 58 evaluable patients, responses were as follows: CR: 1 pt, PR: 18 pts, ORR: 32.7% (95% CI 21-45) with 42% stable disease. TTP and survival results will be presented at the meeting.

Conclusion: Tegafox is an effective regimen with an acceptable tolerance. This regimen should be compared to Oxaliplatin with i.v. 5FU/LV in patients with metastatic CRC. Supported by Bristol-Myers Squibb, France

293 POSTER

Raltitrexed (Tomudex) combined with UFT: a final results phase II study in patients with advanced colorectal cancer (ACRC).

S. Vazquez[1], A. Jimenez-Lacabe[2], G. Perez-Manga[3], J. Feliú[4], G. Quintero[1], J.M. Vieitez[2], J. Nuevo[5], H. Bovio[5], M.L. Garcia-deParedes[5]. [1] *Hospital Xeral Calde, Oncology, Lugo, Spain;* [2] *Hospital Central de Asturias, Oncology, Oviedo, Spain;* [3] *Hospital Gregorio Marañón, Oncology, Madrid, Spain;* [4] *Hospital La Paz, Oncology, Madrid, Spain;* [5] *Astrazeneca Sapin, Medical Departement, Madrid, Spain*

Aims: A Preliminary dose-escalation trial confirmed that recommended dose for the combination of Tomudex (TOM) and UFT are TOM 3 mg/m^2 and UFT 350 mg/m^2.

The primary aim of this study is to assess the efficacy and tolerability of TOM and UFT combination in patients (Pt) with ACRC.

Patients and Methods: Inclusion criteria: Advanced Colorectal Adenocarcinoma, aged $\geq$ 18 years $\leq$ 75, WHO performance status score $\leq$ 2, satisfactory haematological, renal and hepatic function, and at least one assessable or measurable lesion. TOM 3 mg/m^2 was administered as a 15 min. iv infusion, every 3 weeks on days 1 and 21, and UFT (orally three times a day) on days 1 to 28, followed by 2 weeks' rest of a 6 weeks cycle. All Pt who received at least one cycle were evaluated for toxicity and those who received more than 2 cycles were evaluated for efficacy. Response was assessed by imaging techniques and categorised according to UICC Criteria.

Results: From January 2000 to June 2002, 36 Pt were included in 4 Spanish centres. Mean age was 63.6 years (range:44-75). The ECOG at inclusion was: 0 in 8.3%; 1 in 80.6% and 2 in 11.1%. The most common metastases locations were: liver 29 (80.6%), lung 6 (16.7%), and lymphatic node 2 (5.56%). A total of 10 Pt showed 1 metastatic site (33.3%). Another 14 showed 2 metastatic sites (38.9%) and the remaining 12 showed 3 or more metastatic sites (27.8%). A total of 199 Raltitrexed doses were administered, median 5 per patient (range: 1-16). Moderate/severe toxicity grade III-IV was assessed: Neutropenia 11 (30.6%), diarrhoea 8 (22.2%), nausea 3 (8.3%). Efficacy results: Two Pt had a complete response and 10 a partial response, Overall Response 33.3% (C.I.95%: 18.6%-51.0%); 41.7% had stable disease, 8,3% had progressive disease, and 16,6% were non valuable due non-assessment. Median time to progression 26.1 weeks.

Conclusions: Tomudex plus UFT combination is an active treatment in ACRC, obtaining a good objective response percentage, 33.3% and a high percentage disease control, 75.0%. Toxicity is moderate, *neutropenia* being the most frequent event reported.

294 POSTER

Tissue inhibitor of metalloproteinase 3 (TIMP-3) is a new putative target gene in colorectal carcinomas with microsatellite instability (MSI)

W.M. Brueckl[1], J. Grombach[1], W. Dietmaier[2], J. Rueschoff[3], T. Kirchner[4], E.G. Hahn[1], W. Hohenberger[5], A. Wein[1], A. Jung[4]. [1] *Department of Internal Medicine I, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen;* [2] *University of Regensburg, Department of Pathology, Regensburg;* [3] *University of Kassel, Department of Pathology, Kassel;* [4] *Department of Pathology,* [5] *Department of Surgery, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany*

Background/Aim: Microsatellite instability (MSI)is the phenotype of colorectal cancer with a DNA mismatch repair deficiency. Genes with repetitive elements in their coding sequence (CDS) might be target genes for mutations in MSI+ cases. In this study the TIMP-3 gene with a C7 repeat in its CDS was screened for frameshift mutations in colorectal carcinomas. Additionally, the TIMP-3 promotor was analysed for CpG island hypermethylation.

Material/Methods: 40 MSI+ tumours, 20 MSI- cases and 6 cell lines, all previously characterised for MSI status, were selected for this study. The exon 5 of the TIMP-3 gene containing the C7 repeat was analysed for gene mutations using fluorescence PCR followed by capillary electrophoresis. All cases presenting with band shifts in the PCR were sequenced. Additionally, the TIMP-3 promotor was analysed using bisulfite treatment followed by CpG island amplification.

Results: A frameshift mutation could be found in 3 MSI+ tumours and in a colon cancer cell line (SW48). The detected mutations consisted of two insertion-mutations (C8) and two deletion-mutations (C6), respecitely, leading to quantitative and qualitative peptide changes 3' behind the mutation, a region highly conserved during evolution. Additionally, TIMP-3 promotor hypermethylation was present in 2 cell lines and in 11 of 40 (27%) MSI+ tumours.

Conclusions: It could be shown, that the TIMP-3 gene is mutated or methylated in about one third of MSI+ colorectal carcinoma studied. Therefore, it represents a putative new target in tumours of the "mutator-pathway". In combination with recently published data about involvement of MMP-3 and MMP-9 in MSI+ colorectal tumours one might conclude that the family of matrix-metalloproteinases might be of importance for carcinogenesis in the DNA mismatch repair deficient pathway.

295 POSTER

Capecitabine plus irinotecan (CAPIRI) vs capecitabine plus oxaliplatin (CAPOX) as first-line therapy of advanced colorectal cancer (ACRC): updated results of a randomized phase II trial

A. Grothey[1], K. Jordan[1], O. Kellner[1], C. Constantin[2], G. Dietrich[3], H. Kroening[4], L. Mantovani[5], C. Schlichting[6], H. Forstbauer[7], H.J. Schmoll[1]. [1] *University of Halle, Department of Hematology/Oncology, Halle;* [2] *Klinikum Lippe-Lemgo, Lemgo;* [3] *Krankenhaus Bietigheim-Bissingen, Bietigheim-Bissingen;* [4] *Alstadt Hospital, Magdeburg;* [5] *Klinikum St. Georg, Leipzig;* [6] *Diakoniekrankenhaus, Rotenburg-Wuemme;* [7] *Private Practice, Troisdorf, Germany*

Background To assess combining capecitabine (CAP) with irinotecan (IRI) or oxaliplatin (OX) as first-line therapy in ACRC, we performed a randomized phase II trial comparing CAPIRI with CAPOX with optional cross-over after failure of first-line treatment.

	CAPIRI	CAPOX	p-value
N pts	67	75	
Overall response rate (%) (95% CI)	40.3 (28.5-53.6)	50.7 (38.9-62.4)	n.s.
CR (%)	3.0	6.7	
PR (%)	37.3	44.0	
SD (%)	41.8	41.3	
PD (%)	17.9	8.0	
Progression-free survival (months) (95% CI)	7.9 (5.4-9.2)	7.2 (5.7-10.1)	n.s.
% Censored pts	33.3	42.0	
Overall survival (months)	NA	NA	
% Censored pts	67.1	67.9	

Materials and methods: CAP 1000 mg/m2 twice-daily d1-14 plus IRI 100 mg/m2 iv d1, 8 or OX 70 mg/m2 iv d1, 8; q3w. 161 patients (pts) were randomized (median age 63 (33-77), m:f 113:48, CAPIRI 79, CAPOX 82, both arms balanced for age, sex, prior adjuvant, location of primary tumor, number of metastatic sites); 160 pts (CAPIRI 79, CAPOX 81) are evaluable for safety, 142 pts (CAPIRI 67, CAPOX 75) for efficacy. Results from cross-over are currently available for 46 pts.

Results: NCI-CTC grade 3/4 toxicities were equally frequent in both treatment arms (CAPIRI vs CAPOX: diarrhea 12.7 vs 13.6%, nausea/vomiting 6.3 vs 3.7%, infection 3.8 vs 4.9%, cardiac 1.7 vs 1.5%, thrombosis 1.7 vs 1.5%, sensory neuropathy 1.3 vs 6.2%, bilirubin 7.7 vs 7.4%. Four of the first 40 pts in the CAPIRI arm died within the first 60 days after onset of therapy due to septic diarrhea in neutropenia (1 pt), pulmonary embolism (2 pts), and unknown cause (1 pt); subsequently the IRI dose was reduced to 80 mg/m2 d1, 8. Overall, 60-day all cause mortality was 6.3 vs 1.2% (p=n.s.). Preliminary efficacy parameters are detailed in the table below. Dose reduction of IRI did not affect efficacy of CAPIRI. In interim analysis, second-line CAPIRI (CAPOX) achieved CR/PR in 19 (12%) and SD in 47 (44%) of pts.

Conclusions: CAPIRI and CAPOX show substantial efficacy in ACRC. Toxicity profiles are similar with the exception of a higher incidence of early deaths in the CAPIRI arm in the first phase of the trial. Capecitabine appears