grade 3 diarrhea; so this level was determined as MTD. Level 2 was set as RD. A Phase II study is now ongoing and 16 pts were assigned to level 2 up to now. Altogether, 22 patients (including 5 pts with prior CT and 12 pts with adjuvant CT) had received a total of 101 courses and were available for the evaluation of the results. CR was noted in 2 pts and PR in 12 pts, for a response rate of 64% (14/22). Grade 3 leucopenia occurred in 2 pts, G3 anemia in 1 pt, G3 diarrhea in 6 pts, G3 nausea in 5 pts, G3 vomiting in 4 pts. None suffered G4 toxicity.
Conclusion: It was suggested that a combination therapy of 24-hour continuous infusion of CPT-11 and sequential oral UFT/LV appeared to be well tolerated and shows high efficacy for MCRC.

	CPT-11 (mg/m^2/day)	UFT (mg/m^2/day)	LV (mg/body/day)
Level 1	100	233	75
Level 2	100	300	75
Level 3	110	300	75
Level 4	120	300	75

666 PUBLICATION

Anatomical segmentectomy (SGX) is the oncologic equivalent of hemi-hepatectomy (H-HPX) for the treatment of small volume unilobar colorectal liver metastases (CLM)

C. Nesbitt[1], R.J. Glendinning[1], C. Byrne[2], P. Ghaneh[1], G.J. Poston[2].
[1]University of Liverpool, Faculty of Medicine, Liverpool, United Kingdom; [2]University Hospital Aintree, Dept of Surgery, Liverpool, United Kingdom

Introduction: HPX is the only potentially curative treatment for CLM. As methods of detection of CLM and awareness of the benefits of HPX improve, smaller volume disease is being diagnosed increasingly. Historically, most patients underwent H-HPX, but the recent trend is towards more local resections towards increasing hepatic preservation. Furthermore, many patients with initially inoperable disease are now coming to HPX (often SGX) after successful downstaging with systemic chemotherapy. This trend raises questions of oncological benefit, whether this approach increases the risk of residual disease in the ipsilateral remnant liver. This study examines the site of liver only recurrence (LOR) with particular reference to ipsilateral-LOR after unilateral SGX.
Methods: Prospectively collected single centre 5-yr follow-up of 184 patients post-HPX for CLM. Data stratified for type of surgery, survival, LOR (ipsilateral, contralateral, bilateral).

Results

	No. pts	% Op. Mort.	Ipsilat LOR	Contra/Bilat LOR	5 year survival %
Unilat SGX	98	0	13	13	44
Bilat SGX	29	0	–	23	21
Hemi-HPX	27	3	–	15	34
Extended-H-HPX	31	3	–	19	26

5 patients underwent re-HPX for recurrent LOR after unilateral SGX. There were no re-HPX for LOR in any of the other groups.
Conclusions: 13/98 (13%) of LOR were ipsilateral, 29/98 (28%) were contra or bilateral after unilateral-SGX. Since 57/85 (67%) LOR were either contralateral or bilateral following either bilat-SGX or H-HPX, then these data would support the continuing use of unilateral SGX for small volume unilateral CLM.

667 PUBLICATION

Capecitabine and oxaliplatin (XELOX) in combination with bevacizumab in the treatment of metastatic colorectal cancer: results of a phase II trial

J. Bendell, D. Yu, H. Hurwitz, M. Morse, G. Blobe, J. Gockerman, L. Odogwu, M. Mahon, R. Truax, N. Fernando. *Duke University Medical Center, Division of Oncology and Transplantation, Durham, NC, USA*

Background: Bevacizumab (BV) improves survival when added to first-line (5-FU/LV and IFL) and second-line (FOLFOX) chemotherapy for metastatic colorectal cancer (mCRC). The FOLFOX regimen is superior to bolus IFL, but requires the use of an ambulatory infusion pump. Capecitabine, an oral fluoropyrimidine, is a convenient alternative to 5-FU. We designed a phase II trial to investigate the safety and efficacy of capecitabine and oxaliplatin in combination with BV (XeloxA).
Methods: Patients (pts) with untreated mCRC received oxaliplatin 85 mg/m^2 day 1, capecitabine 1000 mg/m^2 bid days 1–5 and 8–12, and BV 10 mg/kg day 1 of a 2-week cycle. The starting capecitabine dose was changed to 850 mg/m^2 bid due to toxicity in the first 27 pts. The primary endpoint was response rate. Safety was analysed for excess 60-day mortality (>15%) or grade 4 adverse events (>50%). Data were analysed using the intent to treat method.
Results: 30 pts have received therapy: 16 men, 14 women; median age 55.2 (range 24–76); all performance status 0. Grade 3 diarrhoea was seen in 30% of pts; no pt experienced grade 4 diarrhoea. Of 3 pts started at the 850 mg/m^2 bid capecitabine dose, none have experienced >grade 1 diarrhoea. Hand–foot syndrome (HFS) was seen in most pts; 6/30 (20%) with grade 1, 12/30 (40%) with grade 2 and 1/30 (3%) with grade 3 HFS. Other toxicities were minimal, including grade 3 neutropenia (7%), grade 3 nausea and vomiting (7%), and grade 3 peripheral neuropathy (10%). 20 pts (66%) required at least one capecitabine dose reduction, and 12/30 (40%) required 2 or more reductions during treatment, typically for diarrhoea and/or HFS. There were 16 partial responses and one complete response (RR 57%; 95% CI: 37–75%); 11 (37%) pts had stable disease. Median TTP was 11.9 months (95% CI: 9.8-∞).
Conclusions: The initial capecitabine dose used in this trial was decreased due to toxicity, primarily HFS and diarrhoea, and appears to be better tolerated. Preliminary evidence suggests that the XeloxA regimen is highly active. This is supported by response data from a randomised phase II trial [Hochster et al. J Clin Oncol 2005;23 (June 1 Suppl): Abstract 3515]. The reported median TTP is among the highest obtained in the first-line treatment of metastatic colorectal cancer. Insights into management of pts on long-term therapy will be reported. Enrollment continues to a planned accrual of 50 pts.

668 PUBLICATION

Concurrent irinotecan, oxaliplatin and uft/lv triple therapy as first-line treatment for advanced colorectal cancer (ACRC)

H.Y. Sheikh[1], J.W. Valle[2], K. Palmer[3], A. Sjursen[4], G. Wilson[2], R. Swindell[4], M.P. Saunders[1]. *[1]Christie Hospital, Clinical Oncology, Manchester, United Kingdom; [2]Christie Hospital, Medical Oncology, Manchester, United Kingdom; [3]Christie Hospital, DCU, Manchester, United Kingdom; [4]Christie Hospital, Statistics, Manchester, United Kingdom*

An open label dose-finding study of concurrent irinotecan (Ir), oxaliplatin (Ox) and oral UFT/LV was conducted in patients (pts) with ACRC. The aim was to find a recommended dose while providing an efficacious treatment in a first-line setting, which was well tolerated by alternating the Ir with the Ox every 2 weeks. All pts received Ir (d1), Ox (d15) and UFT/LV on days 1 to 21 of a 28-day cycle. Using conventional dose escalation criteria, pts were treated in cohorts of 3 and in the absence of grade 3 toxicity (assessed at 1 month), pts were entered at the next dose level (DL). There was no intra-pt dose escalation.

	UFT (mg/m^2/day)	Ir (mg/m^2)	Ox (mg/m^2)
DL-1 (6 pts)	200	180	85
DL-2 (6 pts)	250	180	85
DL-3 (9 pts)	250	180	100
DL-4 (4 pts)	300	180	100

The intended duration of chemotherapy was 24 wks, with response evaluation every 8 wks. 25 pts, median age 63 (range 24 to 79) with WHO PS 0 to 2, were recruited between Feb 2004 to Apr 2005. All pts had measurable disease with a median of 4 marker lesions at baseline (range 1 to 10). At DL-4, 4/4 pts suffered multiple grade 2 toxicities and 3/4 a grade 3 toxicity. Diarrhoea, lethargy and vomiting were the dose-limiting toxicities (DLT). 3 pts were initially entered at DL-3 and a further 6 pts were then entered once the MTD had been reached. At this dose-level, 3/9 pts endured grade 2 toxicities and 1/9 a grade 3 toxicity. One pt (PS 2) who had extensive disease was admitted 5 days after the first dose of chemotherapy (DL-1), with neutropaenic sepsis which was thought to be highly atypical; a question of DPD deficiency was raised. A further pt, also at DL-1, who had demonstrated a PR by RECIST criteria, died from a cardiac event in the third month of treatment. He had no prior cardiac history and no symptoms of angina during the chemotherapy. At this time, 19 pts are evaluable for response giving an ORR of 68% and tumour control rate of 79% (PR- 13, SD- 2, PD- 4). The median duration of response has not been reached. One pt with residual lymph node disease, is awaiting XRT and another patient is awaiting a partial hepatectomy. 6 out of 25 patients have died and as yet the median OS has not been reached. We have established a MTD of Ir 180 mg/m^2 d1, Ox 100 mg/m^2 d15 and UFT/LV 250 mg/m^2/day d1–21 of a 28-day cycle. This combination, which provides a high response rate and a

good side-effect profile, has been used to take further the ongoing phase II trial.
Support to partially fund the trial was provided by BMS.

669 PUBLICATION

Capecitabine and oxaliplatin (XELOX) as first-line treatment for elderly patients (pts) with advanced / metastatic colorectal cancer (MCRC)

A. Salud[1], P. Escudero[2], J. Feliú[3], L. López-Gómez[4], M. Bolaños[5], A. Galán[6], A. Yubero[7], J.M. Vicent[8], F. Losa[9], M. González-Barón[3]. *[1]Hospital Arnau de Vilanova, Servicio de Oncología Médica, Lleida, Spain; [2]Hospital Lozano Blesa, Servicio de Oncología Médica, Zaragoza, Spain; [3]Hospital La Paz, Servicio de Oncología Médica, Madrid, Spain; [4]Hospital Virgen de la Salud, Servicio de Oncología Médica, Toledo, Spain; [5]Hospital San Pedro de Alcántara, Servicio de Oncología Médica, Cáceres, Spain; [6]Hospital de Sagunto, Servicio de Oncología Médica, Valencia, Spain; [7]Hospital Obispo Polanco, Servicio de Oncología Médica, Teruel, Spain; [8]Hospital General Universitario, Servicio de Oncología Médica, Valencia, Spain; [9]Hospital de la Creu Roja, Servicio de Oncología Médica, Barcelona, Spain*

Background: XELOX is a highly active combination in 1st line MCRC, comparable to FOLFOX with less neutropenia and a convenient 3-weekly cycle length. As a well-tolerated, more home-based therapy, XELOX deserves investigation in a more elderly pt population.
Material and methods: Objectives of this phase II study were response rate, safety profile, time to progression and overall survival after XELOX chemotherapy as 1st line treatment in pts aged $\geqslant$70 years with histological confirmation of MCRC. Selection criteria included no prior chemotherapy (except adjuvant therapy), measurable disease according to RECIST, ECOG PS $\leqslant$2 and adequate bone marrow, renal and hepatic function. Patients received oxaliplatin 130 mg/m^2 i.v. D1 followed by oral capecitabine 1000 mg/m^2 twice daily for 14 days (750 mg/m^2 if Cr Cl=30–50 ml/min) every 3 weeks. Toxicity was evaluated according to WHO toxicity criteria.
Results: 50 pts were included: M/F, 36/14, median age 75 years (70–82), ECOG PS 0/1: 54%/46%. 40% of patients presented comorbid disease $\geqslant$1, 74% had mild dependence on help (Barthel Index) and most (M/F 58%/50%) were autonomous (Lawton Index). Median number of metastatic sites was 1 (1 site 78.7%), liver (68.1%), lung (34%) and nodes (12.8%), mainly. Previous treatment included surgery (84%), adjuvant chemotherapy (30%) and radiotherapy (12%). A total of 227 cycles have been administered: median 4.5 (1–8). Median relative dose intensity was 92% for oxaliplatin and 98%/86% (in pts with Cr Cl $\leqslant$50 / Cr Cl >50 ml/min, respectively) for capecitabine. Intent-to-treat efficacy analysis: 5 pts achieved CR, 13 PR, 12 SD, 14 PD and 6 NE (3 toxicity, 1 exitus, 1 lost of follow-up, 1 consent withdrawal), with an ORR of 36% (95% CI: 22.7–49.3). Median follow-up was 10.7 months, median TTP was 5.8 months (95% CI: 3.9–7.8) and median OS was 12.3 months (95% CI: 7.6–16.9). One year survival was 51% (95% CI: 37.0–65.0). There were 1 treatment-related death due to diarrhea and asthenia.
Conclusions: XELOX appears to be effective and well tolerated in 1st line treatment of elderly pts with MCRC.

Grade 3–4 Adverse Events per patient (%)

Diarrhea	22	Febrile neutropenia	2
Asthenia	14	Leukopenia	2
Vomiting	14	Fever	2
Nausea	10	Stomatitis	2
Anorexia	8	Paresthesia	2
Neutropenia	6	Anaemia	2
Thrombocytopenia	6	Abdominal pain	2
Hand–foot syndrome	4	Melaenas	2

670 PUBLICATION

Hepatic arterial infusion (HAI) oxaliplatin and intravenous (i.v.) LV5FU2 after resection of colorectal liver metastases

F. Maire[1], D. Malka[1], D. Elias[2], V. Boige[1], A. Lièvre[1], S. Louafi[1], T. de Baere[3], C. Dromain[4], P. Lasser[2], M. Ducreux[1]. *[1]Institut Gustave Roussy, Department of Medicine, Villejuif, France; [2]Institut Gustave Roussy, Department of Surgery, Villejuif, France; [3]Institut Gustave Roussy, Department of Interventional Radiology, Villejuif, France; [4]Institut Gustave Roussy, Department of Radiology, Villejuif, France*

Background: There is no consensus regarding adjuvant therapy after resection of colorectal liver metastases (LM). The promising response rate of 64% obtained with HAI oxaliplatin and i.v. 5-fluorouracil (5FU) and leucovorin (LV) in patients with unresectable LM (1) prompted us to assess the tolerance and efficacy of this regimen in the postoperative adjuvant setting.
Methods: An HAI catheter was inserted intra-operatively during resection of colorectal LM in patients (pts) at high risk of recurrence (2). All pts had undergone resection of the primary tumor. Adjuvant treatment consisted of HAI oxaliplatin (100 mg/m^2) plus simplified i.v. LV5FU2 (LV, 200 mg/m^2; 5FU, bolus 400 mg/m^2; 5FU, 2400 mg/m^2 48-hour continuous infusion) and was repeated twice monthly for 4 to 6 months. The endpoints were toxicity and survival.
Results: 24 pts (9 men; median age, 54 years; range, 30–68), of whom 21 (88%) had previously received systemic chemotherapy including oxaliplatin or CPT-11, were included. Intra-operative radiofrequency ablation treatment was performed in 14 pts; LM resection was R0 in 21 and R1 in 3 pts. Adjuvant chemotherapy was possible in 19 pts (79%; median number of chemotherapy cycles, 8; range, 3–12). Five pts (21%) did not receive the treatment due to HAI catheter dysfunction (n = 4) or postoperative sepsis (n = 1). Treatment was discontinued due to HAI catheter obstruction or toxicity in one pt each. Grade 3/4 neutropenia or peripheral neuropathy occurred in 26% and 10% of pts, respectively. There were no treatment-related deaths. The 1- and 3-year overall survival rates were 88% and 44%, respectively. The 1- and 3-year extrahepatic recurrence-free survival rates were 66% and 31%, respectively. The 1- and 3-year intrahepatic recurrence-free survival rates were 83% and 66%, respectively.
Conclusion: HAI oxaliplatin and i.v. LV5FU2 is an effective and safe regimen after resection of colorectal LM. Given the low intrahepatic recurrence rate, HAI oxaliplatin should be evaluated in association with more aggressive i.v. chemotherapy in pts at high risk of recurrence.

References

[1] Ducreux M, et al. J Clin Oncol 2005; in press.
[2] Gastroenterol Clin Biol 2003; 27: B41–61.

671 PUBLICATION

Radiation therapy (RT) with concomitant capecitabine and celecoxib followed by surgery in patients with locally advanced cancer of the rectum: A phase II study

M. Kouri[1], R. Huuhtanen[1], T. Joensuu[1], P. Österlund[1], M. Tenhunen[1], P. Luukkonen[2], H. Joensuu[1]. *[1]Helsinki University Central Hospital, Department of Oncology, Helsinki, Finland; [2]Helsinki University Central Hospital, Department of Surgery, Helsinki, Finland*

Background: Preoperative chemo-RT may increase the rate of complete resections (R0) in the treatment of locally advanced rectal cancer. We evaluated the efficacy and safety of preoperative chemo-RT consisting of continuous per oral capecitabine and celecoxib given concomitantly with RT in patients with fixed/locally advanced rectal cancer.
Methods: Patients with fixed or cT4N0–2M0 rectal cancer were eligible. Pretreatment pelvic MRI and/or CT were performed for staging. RT was given using a 3-field technique up to the total dose of 45 Gy/25 fractions, followed by a boost to 9 Gy/5 fractions. Capecitabine 825 mg/m^2 p.o. bid and celecoxib 400 mg p.o. bid were initiated on d. 1 of RT, and capecitabine was discontinued on the last day of RT. Celecoxib was continued until surgery, scheduled to take place 6 weeks after completion of RT. Toxicity was graded according to the NCI CTCAEv3.0 scale. The primary endpoint was pathologic complete response (pCR).
Results: Between January 2003 and May 2005 17 consecutive patients (14 male, 3 female; mean age 56 years, range 40–72 years; WHO PS 0–2) were enrolled. Fourteen patients are evaluable for pCR and toxicity during chemo-RT (Table 1). Two patients had tumour-related abscess requiring drainage (grade 3), one of these patients had a rectoanal fistula and the other one tumour growth to the seminal vesicles prior to therapy.
All patients responded to therapy and surgery could be attempted in all cases. Three (21%) patients had pCR (95% CI 5–50%), and one further