primary tumor was rectum in 12/10 pts; synchronous metastases, 34/25, liver metastases 42/28, >50% involvment 14/8; "2 metastastatic sites 27/23; symptomatic pts A/B 28/25, previous adjuvant chemotherapy 8/8; previous radiotherapy 18/14. Treatment was administred until disease progression, unacceptable toxicity or refusal. We observed 22/91 RC + RP (20%), 15 (31%) in A pts and 7 (16%); SD 15/14, PD 12/13; TTP: A/B 6/5.8; TTF: A/B: 5.2/3.4 mths; median overall survival was 13.8 mths with no difference in the 2 groups A/B 13.8/12.6 mths; median 2-yr OS was 26.6% (A/B; 27.6/25.4). Median OS in CR + PR pts was 25 months with a 2-yr OS of 59% while it was 13 mths in SD pts and (12% at 2 yrs) and 8 in PD pts (22%) ($p < 0.0001$). Multivariate analysis identified RC + RP > PS > liver involvment as independent prognostic factors for survival.

Conclusions: Chrono FUFA is an active regimen in untreated measurable patients and also in those generally excluded from clinical trials. This experience further identifies the emerging role of tumor shrinkage as an indicator of better survival.

222 POSTER

Qualitative and chronological assessment of toxicities during treatment with raltitrexed ('Tomudex') in 861 patients: Implications for patient management

J.E. Garcia-Vargas[1], T. Sahmoud[1], M.P. Smith[1], S. Green[1]. *Zeneca Pharmaceuticals, Alderley Park, United Kingdom*

Introduction: Effective management of drug-related toxicity necessitates a knowledge of the nature and time of emergence of adverse events. Further analysis of the toxicity profile of raltitrexed ('Tomudex') was undertaken to evaluate the incidence, severity and sequence of toxicities in a Phase II and 3 Phase III clinical trials. Patients with aCRC received raltitrexed 3 mg/m^2 by 15-min infusion q21 days. The most frequent toxicities (>5% pts) occurring during the first 10 cycles (6 months) were analysed.

Results: WHO graded toxicities:

	Incidence GI-IV (% pts)	Incidence GIII-IV (% pts)	Early incidence GIII-IV (% pts)		↑Incidence[a] GI-IV (cycle day)
			Cycle 1	Cycle 2	
Non-haematological (n = 861)					
Asthenia[b]	51.1	9.3[c]	3.0[c]	2.4[c]	1–4, 8
Diarrhoea	39.3	11.1	2.6	2.4	1–6
Fever	30.8	1.5	0.6	0.6	2–6
Mucositis	11.3	1.4	0.6	0	None
Nausea/vomiting	65.8	8.1	3.1	1.6	1–9
Pain	44.3	6.2	1.6	1.6	1, 8
Haematological/biochemical (n = 616)					
Anaemia	20.4	6.3	1.1	1.2	5–11, 12–18[d]
AST/ALT ↑	17.9	8.9	2.6	3.6	<5, 12–18[d]
Neutropenia	16.7	11.2	1.8	2.2	5–11, 12–18[d]

[a]Toxicity incidence ≥1%/cycle day or period. [b]Mild, moderate or severe. [c]Severe resulting in withdrawal. [d]Within period specified, dependent on blood sampling time.

Death thought to be causally related to drag treatment occurred in 3.8% of 684 patients receiving raltitrexed in Phase III studies. However, two-thirds of these deaths occurred in the absence of dose reductions specified in the protocols or current dose recommendations.

Conclusions: Toxicities, including diarrhoea and neutropenia, may emerge early during treatment with raltitrexed, and in the 3-week interim period before the following dose is administered. Adequate monitoring should occur and patient vigilance encouraged to ensure early detection of gastrointestinal and haematological toxicities. Patients experiencing these toxicities should be carefully supported with appropriate therapy and either (1) withdrawn from treatment (grade IV or grade III gastrointestinal with grade IV haematological toxicity) or (2) continued on treatment at an appropriate reduced dose following complete toxicity resolution.

'Tomudex' is a trade mark, the property of Zeneca Ltd.

223 POSTER

'Tomudex' (raltitrexed) plus radiotherapy as post-operative treatment or palliative treatment for patients with rectal cancer: Phase I studies

P. Price[1], R. James[2], M. Smith[3]. [1]*Hammersmith Hospital, Dept. of Clinical Oncology, London;* [2]*Christie Hospital, Dept. of Clinical Oncology, Manchester;* [3]*Zeneca Pharmaceuticals, Alderley Park, United Kingdom*

Objectives: Optimal treatment regimens for radiotherapy plus chemotherapy have not been determined in rectal cancer. 'Tomudex' is an alternative to 5FU in patients with advanced colorectal cancer and its radiosensitising effects, acceptable toxicity profile and convenient administration schedule make it an attractive combination candidate for further investigation. Two Phase I dose-escalation studies were initiated to determine the optimal dose of 'Tomudex' in combination with radiotherapy as post-operative adjuvant treatment for patients with operable rectal cancer (adjuvant study) or as palliative treatment for inoperable/recurrent rectal cancer (inoperable study).

Methods: Radiotherapy (50.4 Gy total) was delivered in 1.8 Gy daily fractions 5 times per week for 5–6 weeks in the adjuvant study, and in 2.0 Gy daily fractions 5 times per week for 5 weeks in the inoperable investigation. In both studies, a single dose of 'Tomudex' was administered at least 1 h prior to radiotherapy on days 1 and 22. The planned dose levels of 'Tomudex' were 2.0, 2.6 and 3.0 mg/m[2]. At least 3 patients were to be entered at each dose level. The recommended dose was defined as 1 level below the maximum tolerated dose. Once the recommended dose was defined, at least 6 additional patients were to be entered at this dose level. Toxicity was assessed by monitoring clinical/laboratory findings and adverse events.

Results: The adjuvant study is now complete and, among the 22 patients evaluated for toxicity, DLT was seen for 2/8 patients at dose level 1, 2/11 at dose level 2 and for all 3 patients at dose level 3. Of 19 patients entered in the inoperable study, 2 had a DLT at dose level 2 but the 6 patients entered at dose level 3 have not yet experienced a DLT. This latter study is ongoing and further data will be presented at this meeting.

Conclusions: The recommended dose of 'Tomudex' when combined with post-operative radiotherapy is 2.6 mg/m[2]. The combination of 'Tomudex' plus radiotherapy is feasible, convenient and appears promising for both operable and inoperable/recurrent rectal cancer. 'Tomudex' is a trade mark, the property of Zeneca Ltd.

224 POSTER

Characterization of genetic subtypes of colorectal cancers

O. Csuka, Z. Doleschall, E. Kámory, K. Tóth, I. Péter, I. Köves, P. Rahóty, I. Vámosi-Nagy, Sz. Ottó. [1] *National Institute of Oncology, Budapest, Hungary*

Purpose: The aims of this study is to identify the subgroups of sporadic colorectal cancers with APC or hMLH1, hMSH2 mutations and the further characterization of these subtypes of colon cancers on the basis of the mutation frequencies and expression of p53, TGFBR II, E2F1, E2F4, Cadherin E. Catenin B, p16, Cyclin D genes.

Methods: The mutation and expression of the above mentioned genes have been evaluated in 134 sporadic colorectal cancer and in their normal mucosa by immunohistochemistry, Western blot and PCR-SSCP analysis. The DNA methylation assay of the promoter regions of hMLH1, p16 genes has also been performed by Hpa II, Msp I digested PCR technique.

Results: APC mutations (cd 1450) have been detected in 20% of the tumors. Mutation frequency of hMLH1 and hMH2 was found to be 30% and 20%, respectively. The mt APC tumors contain high level of Cyclin D, E2F1 and low level of p16. P53 mutation could be detected in 45% of mt APC colon cancers. The p53 mutation is infrequent (5%) in the mt hMLH1 tumors. TGFBR II and E2F4 mutations were found in 25% and 40% of mt hMLH1 cases. The hypermethylations of the promoter regions of p16 gene is more frequent in mt APC tumors (30%) than that of the mutant hMLH1 colon cancers.

Conclusions: Our studies might suggest two alternative genetic pathways for sporadic colorectal tumorigenesis initiated by the mutation of APC or DNA mismatch repair genes. The two pathways of colon carcinogenesis could be characterized by different prognostic factors. APC mutated pathway is involved in the upregulation of Catenin B, Cyclin D frequent mutation of p53 and down regulation of Cadherin E. hMLH1 mutated pathway is accompanied by high level of Cadherin E, frequent mutation of TGFBR II, E2F4 gene and low level of Cyclin D and p53, resulting in a favourable clinical outcome of these tumours.

225 POSTER

Randomized phase II study of CPT-11 plus mitomycin C versus oxaliplatin plus mitomycin C in previously treated patients with advanced colorectal cancer (ACC)

H. Ulrich-Pur, S. Brugger, G.V. Kornek, W. Fiebiger, K. Haider, W. Kwasny, D. Depisch, E. Kovats, F. Lang, W. Scheithauer. *Dept. of Int. Med. I, Univ. Medical School, Vienna, General Hospitals of St. Pölten, Wr. Neustadt, Baden, and Neunkirchen, Austria*

Purpose: CPT-11 and oxaliplatin are two new agents with promising activity in ACC. Based on preclinical suggestive evidence that both drugs might act

synergistically with mitomycin C (MMC), the following randomized phase II study using a "pick the winner" design was undertaken.

Methods: 68 patients with ACC cancer who, had received prior palliative 5-FU/leucovorin-based chemotherapy were randomized to either CPT-11 120 mg/m^2 on days 1 + 15 plus MMC 8 mg/m^2 on day 1 (arm A) or oxaliplatin 85 mg/m^2 on days 1 + 15 plus MMC 8 mg/m^2 on day 1 (arm B); in both treatment arms, courses were repeated every 4 weeks.

Results: 57 patients are presently evaluable for treatment response and toxicity. The objective response rate in arm A is 7/30 (23.3%; 95% confidence interval [CI], 9.9 to 42.3%) as compared to 5/27 in arm B (18.5%; 95% CI, 6.3 to 38.1%). Median time to progression and overall survival have not been reached yet. The regimens were not equitoxic as indicated by the incidence of severe adverse reactions requiring dose reductions (40% vs. 11%), treatment delays (25 vs. 10 courses), and early discontinuations (27% vs. 11%) in arm A and arm B, respectively. The most common toxicities in arm A were granulocytopenia (83%), thrombocytopenia (47%), diarrhea (53%), emesis (53%) and alopecia (97%). In arm B, common toxicities included granulocytopenia (56%), thrombocytopenia (74%), emesis (59%) and peripheral neuropathy (41%).

Conclusion: Both combination regimens seem to be effective in 5-FU/LV pretreated patients with ACC, though the observed response activities do not seem to exceed the single agent activity previously reported for CPT-11 and oxaliplatin alone.

226 POSTER

Preoperative chemoradiation plus intraoperative presacral electrons in T3–4 Nx M0 primary rectal cancer: Early single institution experience

F.A. Calvo, R. Cantalapiedra, P. Marcos, E. Del Valle, F. Muñoz, J.L. García-Sabrido, M. Gómez, M.A. Lozano. *Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Purpose: Intense local therapy including intraoperative electron radiotherapy (IOERT) and preoperative chemoradiation has been explored in locally advanced rectal cancer to induce tumor downstaging and promote pelvic disease control.

Materials and Method: From 4/95 to 12/99, 43 T3–4 Nx M0 50 primary rectal cancer patients have been treated with preoperative radiotherapy (45.0 to 50.4 Gy) and simultaneous 5FU (500–1000 mg/m^2 days 1–4 and 22–26) or oral Tegafur (1200 mg/day continous daily through 1 to 28 of radiotherapy). Radical surgery was performed 4 to 6 weeks after the completion of induction tratment and IOERT (10 to 15 Gy) was added to the presacral region. Adjuvant chemotherapy using 5FU and Leucovorin (4 to 6 cycles) was recommended.

Results: Tolerance to treatment was acceptable. Median age was 65 years (range 36–82). There were 34 males and 16 females. Tumor distance from anal verge was less than 5 cm in 15 (30%). Tumor downstaging pathologic findings were: 10 T1, 19 T2, 21 T3–4, 38 N0 and 12 N+, 22 T mic. Sphincter preservation has been achieved in 32 (64%) patients. Median follow-up time is 17 moths. Pelvic tumor control rate is 97%.

Conclusions: Intense local therapy as described is feasible, acceptably tolerated and able to induce significant tumor downstaging effect and encouraging disease control results in primary locally advanced rectal cancer. Up-dated results will be presented.

227 POSTER

A prospective comparison of in-patient versus outpatient DeGramont therapy: Using quality of life, acceptability and response measures: A pilot study

M. Rowe, R. James. *Christie Hospital, Manchester, United Kingdom*

Purpose: Randomised trial data suggest that the 'DeGramont' regimen (DEG) is now the optimal method of administering 5-Fluorouracil (5FU) and folinic acid (FA) for colorectal cancer. However, the regimen requires hospitalisation for 48 hours, every 2 weeks. As part of a feasibility study for a large UK multicentre trial, we initiated a pilot study to compare cost-evaluation and clinical effectiveness of the inpatient (IP) versus outpatient (OP) DEG.

Method: Central line insertion (CLI) for OPs was a day-case procedure by trained nurses. Compliance, costs, response measures and face-to-face quality of life (QOL) were measured in 26 patients given the choice of 12 courses of either IP or OP DEG.

Results: 13 patients were enrolled into each arm. Failure of compliance for the first 6 cycles occurred in 54% IPs compared with 8% OPs ($p = 0.001$). After 12 cycles of DEG 92% OP and 50% IP had stable disease ($p = 0.01$). OP costs were estimated at 50% of bed costs. Treatment delays were significantly more common in IPs mainly due to bed shortages. QOL was significantly superior in OPs.

Conclusion: Three key requirements to convert IP to OP were identified: CLI, prefilled disposable elastomeric infusors; education of patients and/or carers on changing infusors. Factors determining feasibility of OP DE include availability of CLI, patient and clinical preference. We conclude although OP DEG is practical, cost effective and offers considerable QOL benefits, some patients and hospitals may still need IP delivery.

228 POSTER

Disease oriented treatment of metastatic colorectal cancer (CRC) with dose-dense 5-FU/Folinic acid (FU/FA) combination chemotherapy

T.M. Loeffler[1], C. Droege[1], B.H.M. Lenfers[1], T.U. Hausamen[1]. [1]*Städtische Kliniken Dortmund, Dep. of Medicine, Dortmund, Germany*

Treatment of metastatic CRC remains a palliative approach, which should emphasize on quality of life and survival prolongation. Continuous infusion of FU in CRC has been found to be equally effective as FU-Bolus but with significantly reduced hematological and peripheral toxicity. FU as weekly 24-hours continuous infusion up to 2600 mg/m" combined with high-dose FA provides a 3-fold increased dose intensity compared to standard bolus FU/FA protocols, an increased frequency of tumor cell targeting, a favorable toxicity profile and activity in FU/FA pretreated patients. This type of short term and high dose administration of FU was chosen for disease oriented treatment: chemotherapy in case of documented progression (UICC-criteria, including tumor related symptoms), no treatment with stable disease, defined as identical results in two consecutive follow-up procedures. A treatment free progression interval (TFPI) of >5–6 months resulted in administration of the previous protocol, otherwise change to a different combination. Protocols: FU/FA: weekly FA 500 mg/m"/2–4 hrs + FU 2.500 mg/m"/24-hrs; LIF: FU/FA + alpha-Interferon 9 mio I.E. day 1 before FU; MFL: FU/FA + Mitomycin 5–6 mg/m"/24-hrs on day 2. Time schedule: 6 wkly treatments > restaging > continuation for additional 6 wks if no progression of disease > restaging. Patients profile: 115 pts.; median age: 63.4 (37–76); m/w: 74/41; ECOG-Status: 0: 38, 1: 67, 2: 10. Immediate response to treatment (after 12 wkly treatments): CR: 12.6%, PR: 32.2%, NC: 39.1%, PD: 11.5, ND (disease not measurable): 4.6%; response after one TFPI: CR: 4.6%, PR: 13.6%, NC: 43.7%, PD: 29.9%, ND: 8.0%. Median duration of TFPI: 5.0 months (range: 3–27). Median survival in months: all pts: 23.4; no TFPI: 11.0; 1 to n TFPI,s of >3 months: 31.0. Toxicities: no grade III/IV hematologic toxicity, 6/115 with grade III diarrhea, 22/115 with a reversible hand-foot-syndrom and LIF.

Conclusions: disease oriented chemotherapy improves the prognosis for the majority of pts. with metastatic CRC. This strategy focuses for the first time on the patient,s individual tumor biology. Short duration, high dose intensity and frequency of FU administration seems to be essential. Implementation of new drugs (CPT-11, Oxaliplatin) will have additional benefit.

229 POSTER

Prevention and treatment of carcinomatosis from colorectal malignancy

P.H. Sugarbaker. *Washington Cancer Institute, Washington, D.C., United States*

Background: At the time of surgical exploration of the abdomen, approximately 10% of colon cancer patients will be found to have peritoneal seeding. Also, approximately 30% of patients will have disease recurrence within the resection site or on peritoneal surfaces. Phase II studies of peritonectomy procedures and intraperitoneal chemotherapy using mitomycin-C and 5-fluorouracil were employed in an attempt to change the outcome of this clinical situation from a terminal event to long-term survival.

Methods: Patients with primary or recurrent colorectal cancer with peritoneal seeding were evaluated using the Peritoneal Cancer Index (PCI). This is a quantitative prognostic indicator that uses nodule size and distribution to arrive at a numerical score. Also, a Completeness of Cytoreduction Score (CC) based on the extent of cancer following an aggressive cytoreduction was utilized. Other parameters were statistically evaluated.

Results: The PCI was shown to be a prognostic indicator capable of accurately predicting the results of these aggressive treatments ($p < 0.0001$). Also, the CC score had predictive value ($p < 0.0001$). Patients who had carcinomatosis treated in conjunction with a resection of their primary colon cancer showed statistically improved survival over those treated m the setting of recurrent colorectal cancer ($p = 0.02$).