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.

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

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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.

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

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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.

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Characterization of genetic subtypes of colorectal cancers

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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.

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

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