randomly assigned to receive LV5FU2 or FOLFOX4 for 12 cycles. Complete safety data were already presented (deGramont A, ASCO 2002/2003). No excess of thromboembolic events was observed in the FOLFOX4 arm (73 patients) compared to the LV5FU2 arm (87 patients). All cause mortality within one month after end of treatment was similar in both arms (0.5%). Grade 3 sensory neuropathy was observed in 12% of the patients receiving FOLFOX4 with 1% of the patients remaining with grade 3 one year after end of treatment. With a median follow-up of 37 months, a statistically significant improvement in 3-year DFS was observed with the FOLFOX4 combination (78% vs 73%, p<0.01). This translates in a 23% decrease in the risk of recurrence for patients receiving FOLFOX4. The benefit of the Oxaliplatin based treatment was observed in all subsets of patients.

FOLFOX4 is the first regimen that shows superiority over the current standard 5-FU/LV in the adjuvant treatment of colon cancer with a good tolerability.

1086 ORAL

Cetuximab in a randomized phase II trial as a single agent or in combination with irinotecan in patients with Epidermal Growth Factor Receptor (EGFR)-expressing, irinotecan-refractory metastatic colorectal cancer (CRC)

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Background: The EGFR is a valuable target for anticancer therapy. Cetuximab (Erbituxä) is a chimeric anti-EGFR monoclonal antibody, which has shown to be effective in metastatic CRC (Saltz et al, Rothenberg et al, Schoeffski et al: Proc ASCO 2001 and 2002).

Material and methods: The current trial was designed to determine the objective confirmed response rate, the time to progression (TTP) and the survival of the combination of cetuximab plus irinotecan, or of cetuximab as a single agent in patients with EGFR-expressing CRC. Main inclusion criteria were a documented progression on an irinotecan-based chemotherapy, a documented EGFR expression, and a Karnofsky PFS of > 60. Patients in arm A received cetuximab (400 mg/m^2 1st infusion, then 250 mg/m^2 weekly) plus irinotecan at the same dose and schedule on which they had been progressing. Patients in arm B received cetuximab alone with the option to switch to the combination of cetuximab with irinotecan after failure of cetuximab as a single agent.

Results: Of 577 patients screened, 474 EGFR-expressed (82%). 329 patients were randomized in a 2:1 ratio. 218 patients were accrued in arm A (75 female, 143 male, median age 59, 89% with KPS > 80) and 111 in arm B (46 female, 65 male, median age 58, 86% with KPS · 80). The most frequent grade 3/4 adverse events observed in arm A (frequency in arm B is also reported) were diarrhea 20.3% (1.7%), asthenia 12.7% (10.4%), leukopenia 11.3% (0.9%), rash 7.1 (4.3%), and vomiting 6.1% (3.5%). Preliminary evaluation is based on an independent radiological evaluation of the response rate and the TTP. Currently, only approximately 70% of the events for TTP and survival have occurred. According to the intent-to-treat analysis of the trial the observed response rate in Arm A was 22.5% (95% CI 17.1 28.6%), median TTP 4.1 months (m) (95% CI 2.8 4.3 m), and median survival time 8.6 m (95% CI 7.6 9.5 m); in arm B the response rate was 10.8% (95% CI 5.7 18.1%), median TTP 1.5 m (95% CI 1.4 2.0 m), and median survival time 6.9 m (95% CI 5.6 - 9.1 m).

Conclusion: Cetuximab is an effective drug as a single agent and in combination with irinotecan in irinotecan-refractory metastatic CRC. Updated TTP and survival data will be presented at the meeting.

1087 ORAL

Randomized phase III trial of chemoradiation treatment amifostine in patients with colorectal cancer

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Background: Chemoradiotherapy (CRT) is an effective adjuvant treatment for colorectal cancer but can be limited by acute and late toxicities. This multicenter trial investigated whether daily pretreatment with amifostine could reduce the incidence of acute and late gastrointestinal toxicity.

Material and Methods: Patients with colorectal cancer treated by surgical excision were randomized at 1:2 ratio to treatment with CRT alone (n=42) or CRT plus amifostine (A) 300 mg/m^2 daily infusion (n=82). CRT was 5-FU based, given once weekly or during the first and last week of radiation treatment (RT). Patients underwent conventional RT administered as 2Gy/5 days/week to a total dose of 50-60Gy. Blood counts and gastrointestinal acute toxicity were evaluated weekly during concurrent CRT; late toxicity was assessed at 3 months intervals following combined treatment and was graded from 0 to 4 according to the RTOG/EORTC criteria.

Results: There was no significant difference between the treatment arms in patients' baseline characteristics. Patients treated with CRT plus amifostine had a significantly lower incidence of gastrointestinal (grade ≥2) toxicity during treatment (Table below). At 3 months following CRT patients treated with amifostine had a significantly lower incidence of intestinal toxicity 5.6% (4/72) vs. 22.2% (8/36) p=0.0112. Patients were not evaluable for response because of prior surgical intervention.

Conclusions: Amifostine is effective in reducing the incidence of acute and late gastrointestinal toxicity.

1088 ORAL

Irinotecan improves the activity of the AIO regimen in metastatic colorectal cancer: results of EORTC GI group study 40986

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Objectives: EORTC study 40952 demonstrated a significant prolongation of the median progression free survival for the AIO regimen compared to the Mayo-Clinic schedule (5.6 vs 4.0 months, p=0.03) without improvement of survival. The purpose of study 40986 is to assess the efficacy and the safety of irinotecan (IRI) combined with the AIO infusional 5-FU regimen in metastatic colorectal cancer chemonaive patients.

Results: 430 patients were randomised either to receive FA 500 mg/m2 2h plus 5-FU 2.600 mg/m2 24h (AIO) or to receive FA 500 mg/m2 2h plus FU 2.300 mg/m2 24h plus IRI 80 mg/m2 (AIO2.3+IRI) both given weeklyx6, repeated day 50. Due to toxicity, the 5-FU dose was amended to 2.000 mg/m2 24h for AIO+IRI (AIO2.0+IRI). Toxicity grade 3/4 are (AIO, AIO +IRI total and 2.3/2.0g/m) Leukopenia 3%/7%, 8%/6%; febrile neutropenia 1%/3%/5%/2%, diarrhea 21%/29%/36%/24%, stomatitis 1%/3%, 2%/3%; Nausea 7%/8%, 8%/8%; Alopecia (grade2) 2% / 8%, 12%, 5%; any Cardiovascular 9%/8%, 11%/5%. The 60 day mortality rate due to any cause was 3.2% for AIO and 2.3% for AIO+IRI. Objective response rate (AIO vs. AIO+IRI): CR/PR 31.5% vs. 54.2%, p< 0.0001), respectively. Based on recorded deaths (n = 288, 67%) median overall survival (OS) AIO and AIO+IRI are 16.9 (15.3-19.0) and 20.1 (18.0-21.9) months, respectively, p=0.2779. A transient benefit of immediate IRI was observed (p=0.0509, Wilcoxon) with a 1-year survival of 75% vs. 66% and survival curves crossing at around 28 months.

Conclusion: The combination of AIO+IRI is a safe regimen, significantly improves response rate and PFS and also transiently survival. This study

Abstract 1087 – Table: Gastrointestinal Toxicity Grade ≥2 RTOG criteria

	Week 4			Week 5			Week 6		
	CRT+A	CRT	p-value	CRT+A	CRT	p-value	CRT+A	CRT	p-value
Large bowel	15/8020,0%	20/4247,6%	<0.0015	19/7924,1%	21/4250,0%	0.0039	14/5326,4%	9/2142,9%	0.1683
Small bowel	6/807,5%	16/4238,1%	<0.0001	8/7910,1%	17/4240,5%	<0.0001	6/5311,3%	9/2142,9%	0.0041

confirms that infusional 5-FU/FA plus IRI should be considered as a reference treatment in metastatic CRC.

1089 ORAL

Improved safety of capecitabine vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT phase III study)

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Background: tumor-activated capecitabine (X) produced significantly superior response rates and equivalent progression-free and overall survival compared to bolus 5-FU/LV (Mayo clinic regimen, M), with an improved safety profile and fewer hospitalizations in 1st-line metastatic colorectal cancer (n=1207 patients). This high activity, improved safety and patient preference for oral chemotherapy led us to move X forward into the adjuvant setting and compare it to the current global standard, M.

Materials and methods: patients with fully resected Dukes' C colon carcinoma were assigned to oral X (8 cycles of 1250 mg/m^2 twice daily days 1-14, every 3 weeks) or i.v. M (6 cycles of LV 20 mg/m^2 + 5-FU 425 mg/m^2 days I-5, every 4 weeks) for 24 weeks.

Results: a total of 1987 patients from 162 centers in 25 countries were randomised between 11/98 and 11/01. The arms were well balanced for median age (years) [range]: X 60.4 [25-80], M 61.0 [22-82]; ECOG score (% 0/1): X 86/14, M 86/14; sex (% Male/Female): X 54/46, M 54/46; and nodal status (% N1/N2): X 69/30, M 71/29. Overall, 81% of X patients received all 8 cycles and 87% of M patients received all 6 cycles. The most common, related, clinical adverse events (AEs, ≥15% all grades) are presented in the table. X consistently caused less all grade nausea/vomiting, diarrhea, stomatitis and neutropenia, across all age groups (<60, 60-70, >70). X caused less grade 3-4 stomatitis (X 2%, M 15%) and neutropenia (X 2%, M 26%) but more grade 3 hand-foot syndrome (X 18%, M <1%). Grade 3-4 diarrhea (X 12%, M 13%), nausea/vomiting (X 3%, M 3%) and fatigue (X <1%, M 1%) were comparable. Dose reductions for AEs were similar in incidence (X 40%, M 44%) with second dose reduction less common with X (13%), than with M (26%). All-cause, 60-day mortality was X 5 (0.5%) and M 4 (0.4%). Treatment-related deaths were X 3 (0.3%) and M 4 (0.4%).

	Capecitabine (Xeloda®) n=996 All grades (%)	Mayo n=973 All grades (%)	P value
Diarrhea	46	64	<0.001
Nausea/ Vomiting	36	51	<0.001
Stomatitis	22	61	<0.001
Neutropenia	32	63	<0.001
Fatigue/ Asthenia	23	23	0.98
Alopecia	6	22	<0.001
Hand-foot syndrome	61	10	<0.001

Conclusion: in the adjuvant setting oral X has an improved safety profile vs i.v. M, with less diarrhea, nausea/vomiting, stomatitis and alopecia, as seen in metastatic disease. Efficacy data are expected in 2004 after 632 events and if positive would suggest an important role for capecitabine in adjuvant therapy, given these encouraging results and the known patient preference for oral chemotherapy.

1090 ORAL

Continuation of irinotecan (CPT-11) beyond 8 cycles does not improve outcome in patients with advanced colorectal cancer resistant to fluoropyrimidines: results of a phase III multi-centre randomised trial

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Background: Irinotecan (CPT-11) given until disease progression (PD) is an accepted standard therapy for advanced colorectal cancer (CRC) resistant to fluoropyrimidines.

Purpose: To determine whether continuation of CPT-11 beyond 8 cycles improves outcome.

Patients and Methods: Patients (pts) with locally advanced or metastatic CRC and radiological evidence of PD within 24 weeks of completion of fluoropyrimidines were eligible. Pts may have received previous adjuvant chemotherapy and a maximum of 3 lines of palliative chemotherapy. All pts were treated with CPT-11 350 mg/m2 IV over 30 minutes, 3 weekly for 8 cycles, and those with disease response or stabilisation were then randomised to continuation until PD or best supportive care (BSC).

Results: Between 11/97 and 12/02, 333 pts were recruited, of whom 55 pts (16.5%) achieved disease response or stabilisation and underwent randomisation. 230 pts (69%) developed PD, 30 pts withdrew with toxicity, 2 pts refused randomisation and continued CPT-11, and 2 pts were withdrawn. The mean age of randomised pts was 62.4 years (range 42-78). Patient demographics between the 2 arms were well matched. 25 pts, including 6 responders, continued CPT-11 and a total of 277 further cycles were delivered; the median number of cycles delivered was 12 (range 9-20). No further responses were observed after randomisation. The only grade 3/4 toxicity observed was diarrhoea (8%). 30 pts, including 8 responders, were randomised to BSC with 1 remaining in CR. 16 pts with PD received further chemotherapy, of whom 8 received further CPT-11. No difference in progression-free survival (PFS) was observed at 6 months (36.4% for the CPT-11 continuation arm, 95% CI 17.4-55.7 vs 25% for the BSC arm, 95% CI 34.2-71.4; p=0.999). There was no difference in overall survival at 1 year (46.3% for the CPT-11 continuation arm, 95% CI 25.1-65.1 vs 54.8% for the BSC arm, 95% CI 34.2-71.4; p=0.11). No differences in mean global quality of life scores 12 weeks after randomisation were seen (p=0.446).

Conclusion: Continuation of CPT-11 beyond 8 cycles in the small group of patients with disease response or stabilisation does not improve PFS nor OS, nor does it result in significant additional toxicity, or further deterioration in quality of life.

1091 ORAL

How to explain the improvement in survival for colorectal cancer? A French population-based study

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Population-based statistics indicate that colorectal cancer survival has improved over the past 20 years. Little is known about the reasons of this trend. We have previously reported the important role of operative mortality reduction (Mitry et al. Br J Surg 2002; 89:1557-62). The purpose of this work was to study trends in colorectal survival over a 24-year period and to understand the reasons of the improvement in survival beyond the reduction of operative mortality.

Patients et methods: A series of 5,874 cases of colorectal cancers diagnosed between 1976 and 1999 in a well-defined French population were included. Trends in relative survival were estimated.

Results: The dramatic decrease in operative mortality after surgery for cure did not explain all the improvement in survival: after exclusion of operative mortality, the 5-year relative survival rate increased from 49.2 to 56.3 per cent between the 1976-87 and 1988-99 periods (50.3 and 58.0 (p<0.001) in patients under 75 and 47.1 and 53.6 per cent (p<0.001) in patients 75 and over, respectively). Trends were different between age groups. In patients 75 and over there was an increase in the proportion of patients resected for cure from 57.5% (1976-87) to 77.9% (1988-99) associated with an overall improvement in stage at diagnosis. Survival after surgery for cure as well as stage specific survival remained stable indicating that the improvement in survival was in relation with the increase proportion of patients resected for cure. In patients under 75, the increase of patients resected for cure was not the only explanation since there was also an improvement in survival after surgery for cure (from 64.9% to 72.7%, p=0.003) mainly because of the improvement in prognosis of stage III tumours (from 35.7% to 48.6%, p = 0.001). Five-year relative survival did not significantly change for advanced tumours but a significant improvement was observed for 1- and 2-year relative survival in patients under 75.

Conclusion: Trends in survival are very different between age groups. The improvement seen in overall survival for older patients can be attributed to the increase in the proportion of patients resected for cure. For younger patients, there was an increase in the proportion of patients operated for cure but also an improvement in stage-specific survival for stage III tumours suggesting a role for adjuvant chemotherapy. Progress in palliative