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.

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## 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$^2$ 1$^{st}$ 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.

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## 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.

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## 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 |