is relevant to estimate the therapeutic ratio. Failure types occur at different times during FU. The exact occurrence of events is unknown and so the observed data are artificially clustered around the planned visits. If we knew the expected pattern of events, then it would be reasonable to schedule the visits at those times. Since events are related to prognostic factors, the FU visits should be adapted to individual patient characteristics. The aim of this study is to propose a method for defining optimal FU schedules for patients in a resource-efficient way. Data from the CHART bronchus trial are used to illustrate the methods.

Material and Methods: Patients alive without recurrence or serious side effects were scheduled to return at months 2-3, every 3 months to 2 years, every 6 months the next 3 years, then annually. Time to failure and its type (local(LR), distant(DM) or side effects(SE)) were recorded at each visit. Cox proportional hazards models were used to identify prognostic factors associated with each failure type. Competing risks methods were applied to estimate the cumulative incidence functions(CIF), adjusted on prognostic factors. Equally spaced quantiles of CIF were used to estimate the corresponding optimised FU times.

Results: 483 first events were recorded for 542 pts: 114 SE, 162 DM and 207 LR; 59 pts had no event at last FU. The 2-yr CIF rate=89%. Significantly higher risk of failure was observed for males (SE), stage III (DM) and conventional treatment (LR). At the 1st planned visit, the CIF rates were 15%, 13%, 11% and 9% in 4 groups (M-I-IIA, M-III, F-I-IIA, F-III) respectively. 10% failures are expected to occur at 6, 7, 8 and 9 weeks in these 4 groups, with earlier visits for males and later visits for females. Similar methods are used for each 10% CIF quantile. At the 2nd planned visit, 20% cumulative failures are expected to occur at 11, 12, 18 and 18 weeks respectively, etc. These methods allow an adaptation of the FU timing according to tumour site and prognostic factors. This optimisation should result in earlier scheduled visits for certain pts at high risk of failure, which may improve on overall survival. This work formed a part of the REACT programme of ESTRO funded by the EU.

1083 ORAL

Survival is better predicted with a new classification of stage III unresectable non-small cell lung carcinoma (NSCLC) treated by chemotherapy and radiotherapy.

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Background: The 1997 ISS classification separated stage III NSCLC patients into stages IIIA and IIIB. In a previous study including unresectable NSCLC initially treated with chemotherapy, we observed that survival was better predicted when patients were classified into stages IIIbeta (T3-4N3) and IIIalpha (other TN stage III) (Sculier et al, Crit Care Med 2000; 28: 2786). The aim of the study was to validate these results in a further set of patients.

Methods: Stage III unresectable NSCLC patients included in a phase III trial assessing the role of increased dose chemotherapy (SuperMIP: mitomycin 6 mg/m2, ifosfamide 4.5 g/m2, cisplatin 60 mg/m2, carboplatin 200 mg/m2) in comparison to standard chemotherapy MIP (mitomycin 6 mg/m2, ifosfamide 3g/m2, cisplatin 50 mg/m2), before thoracic irradiation (60 Gy in 30 fractions over 6 weeks) are the subject of this study. Survival distributions were assessed by the method of Kaplan-Meier. Survival comparisons were made by the log-rank test. Multivariate analysis using the Cox model, included all potential prognostic factors with a p value < 0.2 in univariate analysis.

Results: According to the 1997 ISS classification, 328 eligible patients were included in the study. There was no imbalance between the 2 arms. For the group as a whole, although a significantly better response rate was observed, there was no survival difference according to treatment arm. Five parameters were significantly associated ($p < 0.05$) with survival in univariate analysis: ELCWP staging (IIIalpha versus IIIbeta), Karnofsky index, weight loss, platelet and haemoglobin counts. These variables as well as the 1997 ISS staging, white blood cell count, LDH and sodium level were included in a multivariate analysis. Two models were constructed, including either the 1997 ISS (model 1) or the ELCWP (model 2) staging systems. In model 1, Karnofsky index (HR = 0.69; 95%CI 0.47-1.00; p=0.05) and haemoglobin (HR = 1.49; 95%CI 1.11-1.99; p=0.007)were significant. Model 2 included 3 covariates: ELCWP staging (HR = 1.68; 95%CI 1.20-2.35; p=0.002), haemoglobin (HR = 1.54; 95%CI 1.15-2.07; p=0.01) and Karnofsky index (HR = 0.72; 95%CI 0.49-1.05; p=0.08).

Conclusion: In unresectable stage III NSCLC treated by chemotherapy and radiotherapy, we validated the results of our previous study. The classification into stages IIIbeta (T3-4N3M0) and IIIalpha (other TN stage III) better discriminates the patients in term of survival than the 1997 ISS classification

Colorectal cancer

1084 ORAL

Only colon cancer patients with Dukes stage C benefit from adjuvant chemotherapy with 5-fluorouracil and levamisole among 425 patients with operable colorectal cancer in a Norwegian randomised study.

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Background: The introduction of adjuvant chemotehrapy for colon cancer with lymph node metastases by Laurie (1) and Moertel (2) was reluctantly accepted by Norwegian medical doctors. We wanted therefore to assess and confirm the role of adjuvant therapy with 5-fluorouracil (5-FU) combined with levamizole (Lev) in a confirmatory randomised study.

Materials and methods: 425 patients with operable colon and rectum cancer, Dukes stage B and C, were from January 1993 to October 1996, included in a randomised multicentre trial in Norway. The age limits were 18-75 years. The trial was approved by the Official Regional Ethics Committee. Therapy started with a loading course of bolus i.v. FU (450 mg/m2) daily for 5 days. From day 28 a weekly iv FU dose (50 mg/m2) were administered for 48 weeks. From day 28 a p.o dose of Lev (50 mg x 3) was sheduled for every 14 days. Totally 214 patients were randomised to 5FU/Lev and 211were included in the control group with surgery alone. Despite some did not met the inclusion criteria (one patient had prior cancer and one had an uterine carcinomars; and 9 actually had Dukes' stage A, one T1, 8 T2), all patients were included in the final analysis on an intention to treat basis. 70% had colon cancer, 30% rectal cancer, and 39% were Dukes' stage C, 59% B and 2% A.

Results: There were no significant difference in the two groups at 5 y: Overall survival was 68.2% in controls and 72.0.8% in the adjuvant group. There were no difference in the two groups when analysed for colon and rectum separately. However, in the subgroup of colon cancer Dukes' stage C the difference in cancer specific survival was significant (p=0.036): surgery alone 47.8%, adjuvant chemotherapy 65.4%.

Toxicity was acceptable: Haematological Gr. 3: 1, Gr 4: 3 and other Gr 3: 33 (mainly diarrhoea and nausea) and Gr. 4: 7 including one infection, among 190 patients where detailed scoring were recorded. No toxic death occurred.

Conclusions: Colon cancer patients with lymph node metastases benefit from adjuvant chemotherapy with FU/Lev and toxicity was acceptable and should continue to receive this therapy as standard therapy.

1085 ORAL

Multicenter international randomized study of oxaliplatin/5FU/LV (folfox) in stage II and III colon cancer (mosaic trial): final results

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FOLFOX4 regimen combining LV5FU2 (leucovorin 200mg/m^2 as a 2-hour infusion, 5-FU 400mg/m^2 bolus and 600mg/m^2 22-hour continuous infusion, d1-2) and oxaliplatin 85mg/m^2 d1, bimonthly, has demonstrated clinical activity in first line metastatic colorectal cancer (de Gramont, J Clin Oncol, 2000, Goldberg, ASCO 2003) as well as in second line (Rothenberg M, J Clin Oncol, 2003). In 1998, we initiated this large randomized phase III study in order to demonstrate efficacy of the FOLFOX4 regimen in earlier stages of the disease with the goal to achieve a 25% decrease in the risk of recurrence at 3 years for patients receiving FOLFOX4 compared to those receiving LV5FU2. From 10/98 to 01/01, 2248 patients with completely resected stage II (40%) or III (60%) colon cancer were

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