	Grade 3	Grade 4	Hospitalized (grade 3–4)
Nausea/vomiting	13	1	4
Diarrhea	33	5	17
Stomatitis	8	–	–
Mucositis	4	1	3
Dermatitis	63	1	–
Infection	7	4	7
Hemorrhage	2	2	3
Thrombocytopenia	5	1	1
Neutropenia	19	9	8
Aplasia	1	5	4
Fistulae	1	4	5
Ileitis RT	2	–	2
Dysuria	5	–	–
Cystitis	5	–	–
IRA	1	–	1
Femoral Artery Occlusion	1	–	–
Ataxia	1	–	–
Dental Abscess	1	–	–
Dyspnea	1	–	–
Pulmonary Embolism	–	3	2
Infarction	–	1	–
Dehydration	–	1	1
Cachexia	–	1	–
Total	**177 (17.5%)**	**39 (3.9%)**	**56 (5.5%)**

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A randomized phase III study (LARCS) comparing preoperative radiotherapy alone versus chemoradiotherapy in non-resectable rectal cancer

M. Brændengen[1,2], K.M. Tveit[3], Å. Berglund[4], E. Birkemeyer[5], G. Frykholm[6], L. Påhlman[7], J.N. Wiig[8], P. Byström[1], K. Bujko[9], B. Glimelius[1,4]. *[1]Karolinska University Hospital, Oncology, Stockholm, Sweden; [2]The Norwegian Radium Hospital, Oncology, Oslo, Norway; [3]Ullevål University Hospital, Oncology, Oslo, Norway; [4]Uppsala University Hospital, Oncology, Radiology and Clinical Immunology, Uppsala, Sweden; [5]Rogaland Central Hospital, Hematology and Oncology, Stavanger, Norway; [6]St. Olavs Hospital, Trondheim University Hospital, Oncology, Trondheim, Norway; [7]Uppsala University Hospital, Surgery, Uppsala, Sweden; [8]The Norwegian Radium Hospital, Surgery, Oslo, Norway; [9]M Sklodowska-Curie Memorial, Radiotherapy, Warsaw, Poland*

Background: Preoperative chemoradiotherapy is considered standard treatment for locally advanced rectal cancer, but there is still limited scientific evidence from randomized studies concerning the value of the chemotherapy in addition to the radiotherapy. This trial investigated if chemotherapy as part of a multidisciplinary treatment approach would improve survival and recurrence rates.
Material and methods: A randomized study of 208 patients in Norway, Sweden and Poland between 1997 and 2003 included patients with locally non-resectable (all T4) primary rectal carcinomas or local recurrences from rectal carcinomas. The patients received either preoperative radiotherapy alone (50 Gy) or chemotherapy (5 FU/leucovorin, Nordic regimen) given concurrently with the same radiotherapy schedule and for 16 weeks after surgery. Surgery was performed 6–8 weeks after the last radiation treatment. All analyses were according to intention-to-treat.
Results: 110 patients were randomized to radiotherapy alone versus 98 to chemoradiotherapy. Radical surgery was performed in 79 (72%) and 82 (83%, p = 0.07) patients and pathological CR was 8% versus 21% (p = 0.04). Local recurrences were seen in 16% versus 12% and distant metastases in 39% versus 27%. Local control, i.e. removed primary and no local recurrence was seen in 66 (60%) versus 73 (74%, p = 0.04) patients. Any grade 3–4 toxicity, mainly gastrointestinal, was seen in 5/110 (5%) and 37/98 (38%), respectively. There were no toxic deaths. Postoperative morbidity and mortality did not differ between groups. Disease–free survival (50% versus 65% at 5 years, log-rank p = 0.05), cancer-specific survival (50% versus 70%, p = 0.03) and overall survival (50% versus 63%, p = 0.1) all favoured the chemoradiotherapy group.
Conclusions: Preoperative chemoradiotherapy results in downstaging, improved resectability and local control in non-resectable rectal cancer versus radiotherapy alone. After a minimum follow-up of one year (median approximately 3 years) there is a marked difference in disease-free and cancer-specific survival (70% at 5 years in the combined treatment group). More grade 3–4 toxicity was seen in the chemoradiotherapy group, but the treatment was generally well tolerable.

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Randomized phase III trial in locally advanced rectal cancer: preoperative chemoradiotherapy with oral uracil and tegafur/leucovorin versus intravenous fluorouracil /leucovorin

M. García Berrocal[1], A. De la Torre[1], F. Arias[2], M. Martín[3], R. Magallón[1], C. Regueiro[1], J. Romero[1], I. Zapata[1], C. De la Fuente[1], R. Hernanz[1]. *[1]Hospital Universitario Puerta de Hierro, Radiation Oncology, Madrid, Spain; [2]Hospital de Navarra, Radiation Oncology, Pamplona, Spain; [3]Centro Oncológico de Galicia, Radiation Oncology, A Coruña, Spain*

Background: Preoperative intravenous fluorouracil (FU) based chemoradiotherapy (CT-RT) is commonly used to treat locally advanced rectal cancer. Oral fluoropyrimidines have been developed as a therapeutic alternative to FU. Based in our previous phase II study report (Int J Radiat Oncol Biol Phys 1999; 45: 629–634), we designed a prospective, multicentric and randomized phase III study to determinate the equivalence of oral uracil & tegafur (UFT)/leucovorin (LV) and FU/LV with concomitant preoperative radiotherapy (RT) in pts with locally advanced rectal cancer.
Material and methods: We randomly assigned pts with cT3-T4 and/or N+ disease to receive either FU (arm A) or UFT (arm B) preoperative CT-RT. Patiens received pelvic RT 45–50.4 Gy (1.8 Gy/day; 25–28 fractions) and concurrent chemotherapy (CT) consisted of bolus FU 350mg/m^2/day and LV 20 mg/m^2/day i.v. days 1–5 and 29–33 (Arm A) or one course of oral UFT 300 mg/m^2/day divided in three doses and oral LV 12.5 mg twice daily days 8–35. Surgery was performed 4–6 weeks after the completion of CT-RT. Adyuvant CT was recommended for N+ pts. The primary end points were pathological response rate and resectability rate. Secondary end points included downstaging rate, toxicity and survival.
Results: Between January 1999 and September 2004, 153 pts from three hospitals were entered in the trial. 77 pts were randomly assigned to arm A and 78 pts to arm B. 76 pts (arm A) and 77 pts (arm B) were included in the analysis of acute toxicity. 71 pts (arm A) and 73 pts (arm B) were included in full analysis. Complete pathological response rate was 13.2% in both arms A and B, and tumor stage downstaging rates were 46.5% and 61.6% respectively (p = 0.07). The resectabilidad rates were 98.6% and 97.3% respectively (p = 0.98). All eligible patients had been followed for a median of 22.7 months (22.1 months-arm A, and 22.7 months-arm B). The 3-year overall survival, disease-free survival and local-relapse free survival was 87% and 74% (p = 0.37), 71.2% and 66.7% (p = 0.33) and 91% and 83% (p = 0.48), respectively. Grade 3 or 4 acute hematological toxicity only occurred in arm A (neutropenia 9.2%, p = 0.023). Grade 3 or 4 diarrhea was 13.2% in arm A and 10.5% in arm B (p = 0.81). Gastrointestinal grade 3 or 4 late toxicity occurred in 2 pts (3%) and 6 pts (8%) respectively (p = 0.27). Treatment related mortality was 5.3% in arm A (2 pts died for acute toxicity, and 2 pts died for gastrointestinal late toxicity) and 1.3% in arm B (1 pts died for post-surgical complications) (p = 0.36).
Conclusions: Preoperative oral UFT/LV based CT-RT in the treatment of locally advanced rectal cancer is at least as effective as i.v. FU/LV based CT-RT, with reduced toxicity. Data from this phase III study support the use or oral fluoropyrimidines with RT in stage II-III rectal cancer.

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Induction chemotherapy (ICT) and dose intensification of the radiation boost in locally advanced anal canal carcinoma (LAACC): Interim analysis of the 101 first randomised patients (pts) in the Intergroup ACCORD 03 trial (Fédération Nationale des Centres de Lutte Contre le Cancer – Fondation Française de Cancérologie Digestive)

D. Peiffert[1], J.P. Gérard[2], M. Ducreux[3], C. Lemanski, E. François, M. Giovannini, F. Cvitkovic, X. Mirabel, O. Bouché, E. Luporsi. *[1]Centre Alexis Vautrin, Radiation Oncology, Vandoeuvre-les-Nancy, France; [2]Centre Antoine Lacassagne, Radiation Oncology, Nice, France; [3]Institut Gustave Roussy, Medical Oncology, Villejuif, France; [4]Centre Val d'Aurelle, Radiation Oncology, Montpellier, France; [5]Centre Antoine Lacassagne, Medical Oncology, Nice, France; [6]Institut Paoli Calmettes, Medical Oncology, Marseille, France; [7]Centre René Huguenin, Medical Oncology, Saint-Cloud, France; [8]Centre Oscar Lambret, Radiation Oncology, Lille, France; [9]Centre Hospitalier Universitaire, Medical Oncology, Reims, France; [10]Centre Alexis Vautrin, Statistics, Vandoeuvre-les-Nancy, France*

Background: Combined radiochemotherapy is the standard treatment of LAACC. The addition of an ICT (Ann Oncol 2001;12:397) and of a higher

dose of irradiation boost (HDRT) are studied in a 4 arms trial (A= ICT, B=ICT+HDRT, C= Reference= Pelvic RT: 45 Gy in 25 fractions with 2 cycles of 5FU-CDDP W1 and W5 and a boost of 15 Gy, D= HDRT). The aim of the study (closed in March 2005, 307 pts included) was to compare the results of the 101 first pts and to assess by an IRC the absence of deleterious effect or initially unpredictable difference between the 4 arms and to confirm the number of pts to be included.

Materials and methods: 101 pts included by 20 institutes in 29 months were analysed. The age was 59 years [range 31–81], the sex ratio was 6/1. All the LAACC were SCC histologic type. There were 3 T1, 55 T2, 22 T3, 20 T4, 1 TX, 57 N0, 18 N1, 24 N2–3, 2 NX. The T size was <4 cm in 26 pts and ⩾4 cm in 69 pts, ND 6 pts. The 4 arms were well balanced concerning the sex ratio, age, stage, T size, differentiation.

Results: One violation of the protocol was noticed (metastatic disease). The tolerance to the treatment was similar in the 4 arms (3 toxic deaths, 4 pts did not receive the irradiation boost). A CTC grade 3–4 toxicity was described 27, 33, 23, 19 times in the arms A, B C, D, respectively. The compliance to the treatment was: 99% for ICT, 100% for pelvic RT-CT (median dose= 45 Gy), and 96% for the boost. The tumour complete (and partial) responses at 2 months were: A: 84% (96%), B: 90% (100%), C: = 78% (87%), D: = 78% (100%), (NS).

The median follow-up was 36 months [1–62]. Overall local failures were 23%: arm A: 32%, arm B: 9.%, arm C: 27%, arm D: 19%. The actuarial results at 3 years were:

Local control (82.5%): arm A: 71%, B: 95%, C: 80%, D: 88%.

Event free survival (74%): arm A: 73%, B: 76%, C:71%, D:65%.

Overall survival was 78%. The causes of the 24 deaths were the cancer in 16 pts (A: 7 pts, B: 1 pt, C: 4 pts, D: 4 pts), 3 treatment related deaths, and 3 intercurrent deaths. The actuarial colostomy free survival was 82% at 2 years: A: 74%, B: 85%, C: 88%, D: 84%.

Conclusion: This intermediate analysis assessed the good tolerance of the intensification of the treatment of LAACC by an ICT and a HDRT. The absence of deleterious effect or unexpected significant improvement by the intensification of the treatment confirmed the necessity to include more than 300 pts, to be able to obtain a significant difference.

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Safety, tolerability and efficacy of the addition of bevacizumab to oxaliplatin/fluoropyrimidine regimens as first-line treatment of metastatic colorectal cancer (mCRC): Results of TREE 2 cohort of the TREE study

H. Hochster[1], L. Hart[2], R.K. Ramanathan[3], J. Hainsworth[4], S. Griffing[5], R. Mass[5], Y. Nagarwala[6], G. Jirau-Lucca[6], A. Shpilsky[6], B.H. Childs[6].
[1]NYU Cancer Institute, Medical Oncology/Clinical Pharmacology, New York, USA; [2]Florida Cancer Specialists, Medical Oncology, Fort Myers, USA; [3]University of Pittsburgh Cancer Center, Medical Oncology, Pittsburgh, USA; [4]Sarah Cannon Cancer Center, Medical Oncology, Nashville, USA; [5]Genentech, Inc, Oncology, South San Francisco, USA; [6]Sanofi-Aventis, Oncology, Bridgewater, USA

Background: The addition of bevacizumab (Bev) to fluorouracil (FU)-based combination chemotherapy results in statistically significant improvement in survival among patients (pts) with metastatic colorectal cancer *(Hurwitz H et al. NEJM 2004; 350:2335–2342)*. The TREE study was designed to assess the safety, tolerability and efficacy of each of three oxaliplatin (OX) plus fluoropyrimidine (FP) regimens (bolus (b), infusional or oral FP; in the TREE-2 cohort, Bev 2.5 mg/kg/week was added to each regimen.

Materials and methods: Eligibility: age ⩾18; measurable untreated mCRC; PS = 0–1. **Primary endpoint**: Grade 3–4 toxicities in the first 12 weeks of treatment; **Secondary endpoints**: RR, TTP, and OS. The regimens in mg/m^2 were: m**FOLFOX+Bev** = O 85, Leucovorin (LV) 350 mg, 5FU bolus 400 & 2400 CIV x 46 hrs and Bev 5 mg/kg q 2 wk; **bFOL+ Bev** = O 85 days (d) 1&15, LV 20 & bolus 5FU 500 d 1, 8, 15 q 4 wk and Bev 5 mg/kg q 2 wk; **CapOx+Bev** = O 130 d 1, Capecitabine 850 x 14d and Bev 7.5 mg/kg q 3 wk.

Results: 223 pts were randomized; 213 were treated. Selected grade 3–4 toxicity during first 12 weeks of treatment is shown in the table. To date, the major reason for discontinuation in each arm has been development of adverse events (AE), but the time to discontinuation appears to be comparable to other clinical trials utilizing similar OX-containing regimens. Confirmed overall RR in treated patients was: **mFOLFOX+Bev** 52%, **bFOL+Bev** 34%, **CapOx+Bev** 45%. 49% of pts would be censored at this point, 5% of pts are still on study treatment; accordingly, corresponding TTP data are not yet mature, which may be a sign of potential prolongation of TTP due to addition of Bev vs. non-Bev regimens.

Conclusions: Treatment with Bev + mFOLFOX is tolerable, with a promising RR in this patient population, particularly as compared to the TREE-1 cohort (Proc ASCO GI, 2005). Grade 3–4 toxicity with first line Bev plus OX based chemotherapy is less than that reported with Bev + IFL. All regimens of FP administration are active in combination with Bev but mFOLFOX appears to have the best balance of response and toxicity. We await additional confirmation of efficacy as determined by median TTP.

Events	mFOLFOX-Bev N = 71 (%)	bFOL-Bev N = 70 (%)	CapeOx-Bev N = 72 (%)
Vomiting	1	11	7
Dehydration	6	11	8
Diarrhea	10	26	17
Neutropenia	35	13	4
Febrile neutropenia	3	1	0
Hand–foot syndrome	0	0	7
Neurotoxicity	3	4	7
Hypertension	9	4	10
Bleeding	0	4	1
Thrombosis (arterial)	0	0	1
Proteinuria	0	0	1
Any Grade 3 or 4	65	60	58

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Safety analysis of first-line bevacizumab plus chemotherapy in patients with metastatic colorectal cancer (mCRC) participating in a US registry

M. Kozloff[1], A. Cohn[2], N. Christiansen[3], P. Flynn[4], F. Kabbinavar[5], R. Robles[6], M. Ulcickas-Yood[7], S. Sarkar[8], J. Hambleton[8], A. Grothey[9].
[1]Ingalls Hospital, Harvey, IL, USA; [2]Rocky Mountain Cancer Centers, Denver, CO, USA; [3]South Carolina Oncology Associates, PA, Columbus, SC, USA; [4]Park Nicollet Clinic Cancer Center, St Louis Park, MN, USA; [5]UCLA School of Medicine, Los Angeles, CA, USA; [6]Bay Area Cancer Research Group, Concord, CA, USA; [7]EpiSource, LLC, Hamden, CT, USA; [8]Genentech Inc, South San Francisco, CA, USA; [9]Mayo Clinic, Rochester, MN, USA

Purpose: Data showing that bevacizumab (BV) increases overall survival when used first line in combination with 5-FU/LV +/– irinotecan to treat mCRC [Hurwitz et al. NEJM 2004; 22: 2335–42; Mass et al. JCO 2004; 22 (July 15 Suppl): abstract 3616] led to US approval early in 2004. Data indicate that certain serious adverse events, including GI perforations, occur rarely but more frequently in patients treated with BV + chemotherapy (CT) than those who receive CT alone. The US FDA has approved bevacizumab for use with all 5-FU-based CT regimens, including FOLFIRI and FOLFOX. A surveillance registry (BRiTE) was opened after US regulatory approval to evaluate safety in clinical practice.

Methods: BRiTE was opened in February 2004. Planned enrolment is 2,000 patients with mCRC receiving first-line BV + CT. Choice of CT regimen is at physician discretion. Eligibility criteria were minimised to promote enrolment of a broad mCRC population. Data on history of hypertension, stroke or myocardial infarction, diabetes, hypercholesterolemia, atrial fibrillation, chronic anticoagulant or aspirin use, peptic ulcer disease, diverticulosis, and recent surgery or endoscopy are collected at baseline. Patients are followed for up to 3 years. Clinical data (including survival, disease progression and adverse events) are collected every 3 months.

Results: As of March 2004, 1367 patients (median age 63 [range 22–92]; PS 0–1 85.5%; primary colon cancer 80.1%) had been enrolled at 273 US sites. The most common first-line CT regimens used with BV are FOLFOX (49.8%), FOLFIRI (15.0%), IFL (11.9%) and bolus 5FU/LV (7.8%). 541 patients have had a 3-month assessment and 420 a 6-month assessment. Among the 1367 patients enrolled, BV-related serious adverse events have been reported in 110 patients (8.0% of enrolled patients). These include 22 GI perforations (1.6%) and 7 post-operative hemorrhages or wound-healing complications (0.5%); other reported events include venous (2.0%) and arterial (0.4%) thromboembolic events.

Conclusions: In patients with mCRC treated with BV in combination with various CT regimens, the safety profile of BV appears to be consistent with that observed in clinical trials, suggesting that it is feasible to combine BV with regimens such as FOLFIRI and FOLFOX. The latter combination has recently been shown to improve survival in a phase III study [Giantonio et al. JCO 2005:23 (June 1 Suppl): Abstract 2]. Recruitment will close on June 30, 2005; updated data will be presented.