**Methods:** From 16 May 2003 to 31 August 2004, 177/304 pts have been randomized to receive either XELOX (91 pts: X 1000 mg/m$^2$ bid d1–14, oxaliplatin 130 mg/m$^2$ d1, q3w, maximum 8 cycles) or FOLFOX-6 (86 pts: 5-FU 400 mg/m$^2$ i.v. bolus then 2400–3000 mg/m$^2$ 46-hour infusion, LV 400 mg/m$^2$ 2-hour infusion, oxaliplatin 100 mg/m$^2$ d1, q2w, maximum 12 cycles).
**Results:** Baseline pt demographics were comparable in the XELOX vs. FOLFOX-6 arms: M/F (60%/40% vs. 62%/38%); median age: 65 (range32–83) vs. 63 (45–84). 91% of pts in the XELOX and 93% in the FOLFOX-6 arms had ECOG PS 0–1. Other baseline characteristics were well balanced. To date a median of 6 XELOX cycles (range 1–8) and 11 FOLFOX-6 cycles (range 1–12) have been administered. It is important to note that 1 cycle of XELOX = 3 weeks and 1 cycle of FOLFOX-6 = 2 weeks. Clinical adverse events were acceptable and generally similar in the XELOX and FOLFOX-6 arms (see table). There was a similar rate of diarrhea, nausea, vomiting and fever in both groups. XELOX led to more hand–foot syndrome, but less neuropathy, asthenia, alopecia and stomatitis. There was a similar rate of grade 3/4 diarrhea, nausea, vomiting, fever and asthenia in both groups. XELOX led to less grade 3/4 paresthesia and neuropathy. One toxic death was reported in each arm. Pts receiving XELOX experienced less grade 3/4 neutropenia and more thrombocytopenia than those on FOLFOX-6.
**Conclusions:** These data show that XELOX and FOLFOX-6 are well tolerated in first-line MCRC. If the final results from this study confirm this preliminary analysis, XELOX offers benefits to the pt in terms of clinical safety. The planned enrollment of 304 pts is now complete and updated safety results will be reported at the meeting.

| | % of pts with Adverse events (NCIC-CTC grade) | | | |
|---|---|---|---|---|
| | XELOX (n = 91) | | FOLFOX-6 (n = 86) | |
| | 1/2 | 3/4 | 1/2 | 3/4 |
| Diarrhoea | 47 | 9 | 45 | 7 |
| Hand–foot syndrome | 19 | 0 | 12 | 0 |
| Nausea | 54 | 2 | 62 | 2 |
| Vomiting | 36 | 3 | 36 | 1 |
| Asthenia | 31 | 9 | 54 | 7 |
| Neuropathy | 11 | 1 | 11 | 11 |
| Paresthesia | 63 | 3 | 65 | 14 |
| Anaemia | 13 | 2 | 19 | 5 |
| Neutropenia | 21 | 6 | 16 | 49 |
| Thrombocytopenia | 12 | 14 | 50 | 6 |

**637** POSTER

**CAPOX vs CAPIRI in combination with concomitant boost 3D-conformal radiotherapy in neoadjuvant treatment of locally advanced rectal cancer**

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**Background:** Several randomised trials have demonstrated the role of preoperative chemo-radiotherapy in the treatment of local advanced rectal cancer to reduce the rate of local recurrence, but there is no agreement on the chemotherapy and radiotherapy schedule. The aim of this study is to compare the combination of oral Capecitabine with Oxaliplatin or Irinotecan (CPT-11) in association with high dose radiation therapy.
**Patients and methods:** Thirty-three patients (21 males/12 females, median age 59 years and ECOG-PS 0–1) with a histologically proved uT3–4 N-/+ or uT2 N+ rectal cancer entered the study, from January 2003 to December 2004. No patient showed systemic disease at the time of diagnosis. They were randomly assigned to receive Oxaliplatin 130 mg/m$^2$ on days 1, 22 and 43 (17 pts, CAPOX GROUP) or Irinotecan 180 mg/m$^2$ on days 1, 22 and 43 (16 pts, CAPIRI GROUP) in combination to Capecitabine 1250 mg/m$^2$ bid days 1–14 and then 825 mg/m$^2$ bid on days 22–55, concomitant with radiotherapy started on day 22. The radiotherapy was administered to the whole pelvis to a dose of 45 Gy (1.8 Gy/fraction), with a concomitant boost to the CTV to a dose of 9 Gy (1.5 Gy/fraction, during the last 6 days of treatment with a 6-hour inter-fraction interval): the total dose to the primary tumor was 54 Gy with a 3D-conformal technique. Surgery was carried out 6–8 weeks after the completion of chemo-radiation by the same surgical team.
**Results:** Among all treated patients, in one patient in CAPIRI GROUP the chemo-radiation treatment was discontinued for GI toxicity and the patient came out the study; the other 32 pts received 95% and 92% of the planned chemotherapy dose, respectively 17 pts in CAPOX GROUP and 15 CAPIRI GROUP. The dose-limiting toxicity was grade III-IV diarrhoea, occurring in 1 pt (CAPOX GROUP) and 3 pts (CAPIRI GROUP). Neurotoxicity was very limited, as only 5 patients experienced grade I toxicity in CAPOX GROUP. A clinical and pathological downstaging was detected in 12 pts (70%) in CAPOX GROUP and 11 pts (73%) in CAPIRI GROUP. A complete pathological remission was seen in 4 pts (23%) in CAPOX GROUP and 4 pts (26%) in CAPIRI GROUP. Twenty-three patients (72%) underwent sphincter-saving surgery, 12 (70%) in CAPOX GROUP and 11 (73%) in CAPIRI GROUP; nine patients were treated with Miles abdomino-perineal resection. All patients are alive after a median follow-up of 16 months (range 2–24 months), but 4 of them, equally distributed in the two groups, developed distant metastases.
**Conclusions:** both CAPOX and CAPIRI are feasible and effective, resulting in excellent results, comparable to those of best series of neoadjuvant treatment. CAPOX was better tolerated than CAPIRI, as diarrhoea was more frequently associated with Irinotecan infusion. Moreover, it was reported an increased radio-chemo induced-fibrosis in CAPIRI GROUP. Further studies are needed to assess the superiority of a particular treatment schedule.

**638** POSTER

**Distal clearance margin less than 9 mm: a safe margin in rectal cancer patients**

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**Background:** Recent reports suggest that a distal clearance of 10 mm at the lower surgical margin may be considered adequate in the surgical treatment of rectal cancer.
**Methods:** We report the experience of the National Cancer Institute of Milano (Italy) in the treatment of low rectal cancer with the technique of total rectal and mesorectal resection (TRR) with coloendoanal anastomosis (CEAA). Between March 1990 and December 2002 we performed 557 consecutive TRR and CEAA at our Institute. 178 patients of this series with a minimum follow up of 18 months (mean 61 months) were treated for a primary cancer without preoperative chemoradiotherapy.
There were 94 patients with distal clearance margin (DCM) <9 mm and 84 with DCM >10 mm. Each group was stratificated by pathological stage and nodal status. The local recurrence subsets was stated. All B2 and C1–2 Astler Coller stage patients in this series received post operative chemo-radiotherapy.
**Results:** see table.
**Conclusions:** Our data suggest that the distal clearance margin of resection less than 9 mm eventually in combination with post operative chemo-radiotherapy do not affect local recurrence rate in N0 and N+ patients.

Table 1. Number of events by DCM group.

| | DCM | | | |
|---|---|---|---|---|
| | Negative ⩾1 cm | | Negative <1 cm | |
| | No. | % | No. | % |
| Total subjects | 84 | 41.4 | 94 | 46.3 |
| **First event:** | | | | |
| Local relapse | 6 | 7.1 | 7 | 7.5 |
| Distant metastasis | *15 | 17.9 | *21 | 22.3 |
| Second malignancy | 3 | 3.6 | – | – |
| NED death | 7 | 8.3 | 2 | 2.1 |
| Deaths | 28 | 33.3 | 16 | 17.0 |

DCM: Distal Clearance Margin; * One distant metastasis was concurrent with local relapse

**639** POSTER

**Phase I/II study of PTK/ZK, a novel, oral angiogenesis inhibitor in combination with FOLFIRI as first-line treatment for patients with metastatic colorectal cancer**

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**Background:** Vascular endothelial growth factors (VEGFs) and VEGF receptors (VEGFRs) are important mediators of tumor growth and metastasis, and their expression is associated with poor prognosis in

patients (pts) with metastatic colorectal cancer (mCRC). PTK/ZK is a novel, oral, angiogenesis and lymphangiogenesis inhibitor that blocks tyrosine kinase signaling from all known VEGFRs.
**Methods:** This trial determined the maximum tolerated dose and dose-limiting toxicity (DLT) of once-daily oral PTK/ZK in combination with infusional 5-fluorouracil (5-FU)/leucovorin (LV) plus irinotecan (FOLFIRI) as first-line treatment in pts with mCRC. PTK/ZK was administered orally, once daily in escalating doses of 500, 1,000, 1,250, and 1,500 mg/day to cohorts of 3 to 7 pts. FOLFIRI was administered every 2 weeks as irinotecan (180 mg/m$^2$, day 1) plus LV (200 mg/m$^2$, 2-hour infusion) and 5-FU (400 mg/m$^2$ bolus followed by 600 mg/m$^2$ as a 22-hour infusion) on days 1 and 2.
**Results:** To date, 21 pts have been enrolled at 500 (n = 6), 1,000 (n = 7), 1,250 (n = 5), and 1,500 (n = 3) mg/day. PTK/ZK was well tolerated; commonly reported grade 1/2 adverse events were nausea, diarrhea, fatigue, vomiting, epistaxis, and dizziness. There was 1 DLT at 500 mg/day (grade 3 fatigue) and 1 at 1,000 mg/day of PTK/ZK (grade 3 hypertension); both resolved within 2 weeks of PTK/ZK discontinuation. The pharmacokinetics of PTK/ZK was unaffected by FOLFIRI. Coadministration of 1,250 mg/day PTK/ZK with FOLFIRI had minimal effect on irinotecan exposure, but lowered the area under the curve (AUC) of the active metabolite SN-38 in serum by ~40%; the clinical relevance is under investigation. Best response (by Southwest Oncology Group [SWOG] criteria) to date for 20 evaluable pts included 11 (55%) partial responses, 7 (35%) had stable disease, and no pts had progressive disease; 2 pts were not evaluable. Median progression-free survival for 20 pts was 7.1 months (95% CI = 6.2, 11.7 months).
**Conclusion:** These preliminary results suggest that the combination of PTK/ZK with FOLFIRI is safe, well tolerated, and has activity in pts with mCRC. Based on these findings, the 1,250 mg/day dosing cohort will be expanded by 24 pts.

**640** POSTER

**Topography and natural history of pelvic recurrences from rectal cancer treated with preoperative chemoradiation and intraoperative presacral electron boost**

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**Purpose**: To analyze the pelvic anatomic pattern of recurrence and its clinical behaviour in rectal cancer intensively treated with neoadjuvant chemoradiation (CRT), radical surgery and adjuvant presacral intraoperative electron boost.
**Patients and methods:** From 5/1995 to 3/2003 154 consecutive patients (p) entered in the IOERT institutional adjuvant program for locally advanced rectal cancer (85% $T_3$, 10% $T_4$, 45% $N_+$). Preoperative treatment consisted in 4500–5040 cGy pelvic radiation with simultaneous 5FU iv continuous infusion (45 p), oral Tegafur 1200 mg/day (65 p), or two courses of neoadjuvant Oxaliplatin+5FU (FOLFOX4) followed by concomitant CRT with oral Tegafur (47 p). Radical surgery was performed 4–6 weeks after the completion of CRT. IOERT was delivered to all of patients over the presacral space, using circular applicators from 5 to 9 cm (beveled end angles of 30º and 45º degrees). The IOERT doses ranged from 1000 to 1500 cGy (mean 1250 cGy). Adjuvant systemic chemotherapy was electively administered to 66% of patients.
**Results**: Median follow-up time for the entire group was 40 months. Pelvic recurrences had been pathologically documented in 10 p (6%), 5 p were $_pT_3$ stages and 4 p were $_pN_+$ stages. Median time for pelvic recurrence diagnosis was 25 months (range 7 to 52 months). Anatomic topography within the pelvic area was: presacral (2), anastomotic (6), posterior vaginal wall (1) and hypogastric nodes (1). Timing of pelvic recurrences identified 4 isolated relapses, 1 sincronous (lung metastases) and 5 methacronous (liver, lung, retroperitoneum and CNS metastases). Rescue treatment for local relapses was atempted in 4 p. Outcome of p with local recurrences showed 2 p alive with disease (at 33 and 89 months), 1 p NED after surgical rescue (at 56 months) and 7 cancer related deaths.
**Conclusions:** Moderate Intraoperative presacral electron boost in the context of preoperative CRT minimizes the risk of topographic recurrence in the posterior pelvic cavity (1%), whereas peri-anastomotic tissues emerge as the new dominant site for pelvic recurrence (60%), offering potential opportunities for rescue treatment of radical intent.

**641** POSTER

**A phase II trial of Capecitabine (X) and Irinotecan (I) in a biweekly schedule in patients with untreated advanced colorectal cancer (ACRC)**

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**Background:** Capecitabine (X) and Irinotecan (I) combination has been shown to be synergistic in ACRC. We conducted a phase II study of IX combination for previously untreated patients with measurable ACRC to evaluate the objective response rate and the safety profile. Secondary objectives were time to progression (TTP) and overall survival (OS).
**Methods:** Patients with histologically confirmed locally advanced or metastatic CRC, measurable disease, ECOG PS ⩽2 and adequate bone marrow, renal and hepatic functions were included. Previous adjuvant chemotherapy was allowed if finished ⩾6 months before starting study treatment. Patients received I 175 mg/m$^2$ on D1 as a 30-min iv infusion and X 1000 mg/m$^2$ twice daily po from D2–8. For patients >65 years, the dose of I and X were reduced to 140 mg/m$^2$ and 750 mg/m$^2$ twice daily, respectively. Cycles were repeated every 14 days until progressive disease, unacceptable toxicity or consent withdrawal.
**Results:** 45 patients were enrolled (M/F, 35/10). Median age was 67 y (42–80). Twenty-five (56%) patients were >65 y. ECOG PS 0–1: 93% of patients (42/45). Primary tumor sites were colon 51% (n = 23), rectum 47% (n = 21) or both 2% (n = 1). Median number of metastatic lesions was 2 (64% with ⩾2 sites) in liver (64%), lung (27%), peritoneum (13%), lymph nodes and bone (7%) and skin (3%). Previous treatment included surgery (73%), adjuvant chemotherapy (44%) and radiotherapy (20%). To date, 408 cycles (median 10, range 2–12; ⩽65/>65 184/224) were administered. Median relative dose intensity was 94% for X and 99.5% for I (85 and 99%, respectively, for patients >65 y). All patients were evaluable for toxicity (see table below). 38 pats have been evaluated to date: 3 achieved CR (7.9%, 2–21%), 16 PR (42.1%, 26–59%), 14 SD (36.8%, 22–54%) and 5 progressed (4–28%) resulting in an ORR of 50% (CI 95%: 33–67) and tumor growth control (RR + SD) in 87% of patients (CI 95%: 72–96). Median TTP and OS were not achieved yet.
**Conclusions:** X and I, in a biweekly schedule as first line treatment of locally advanced or metastatic CRC is an active schedule with a manageable toxicity profile, even in patients >65 years.

| Toxicity gd. 3–4 | Pat. ⩽ 65 (184 cycles) | Pat. >65 (224 cycles) |
|---|---|---|
| Thombopenia | 0 | 1 (0.5%) |
| Neutropenia | 2 (1.1%) | 2 (0.9%) |
| Alopecia | 5 (2.7%) | 0 |
| Nausea and vomiting | 0 | 3 (1.3%) |
| Diarrhea | 1 (0.5%) | 7 (3.1%) |
| Asthenia | 3 (1.6%) | 9 (4.0%) |
| Other | 2 (1.1%) | 4 (1.8%) |

**642** POSTER

**Cetuximab plus oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) for the epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer (mCRC) in the first-line setting: a phase II study**

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**Background:** The EGFR is highly expressed in mCRC and is commonly associated with more aggressive disease and resistance to radiotherapy. Cetuximab (Erbitux®) is an IgG1 monoclonal antibody (MAb) that specifically targets the EGFR. FOLFOX-4 is a standard option for the first-line treatment of mCRC. The aim of this phase II study was to investigate