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