0 (21.2% total no. pts), 1 (57.6%), 2 (21.2%); n° metastatic sites: 1 (9.1%), 2 (48.5%), 3+ (42.4%).

Dose level	Raltitrexed (mg/m²)	UFT (mg/m²)	No. pts	DLT (G3/4)	Toxicity	Objective Response
1	2.0	200	3	0		1 PR, 1 SD, 1PD
2	2.5	250	6	1	1 pts Diarrhoea (G-3)	1 PR, 4 SD, 1 PD
3	2.5	300	3	0		1 PR, 2 SD
4	3.0	250	3	0		1 PR, 2 SD
5	3.0	300	6	1	1 pts Diarrhoea (G-3)	3 PR, 3 SD
6	3.0	350	6	2	1 pts Mucositis (G-3) 1 pts Neutropenia (G-3)	1 PR, 3 SD, 2 NA
7	3.5	300	6	3		

PR: Partiel Response; SD: Stable Disease; PD: Progresion Disease; NA: Not Avalaible. DLT was Diarrhoea, vomiting and neutropenia at level 7.

Conclusions: These results confirm that recommended dose for the combination of Raltitrexed and UFT is the same as recommended doses for monotherapy, Raltitrexed 3 mg/m², every 3 weeks on days 1 and 21, and UFT 350 mg/m², on days 1 to 28, followed by 2 weeks' rest of a 6 weeks cycle.

'Tomudex' is a trademark, the property of the AstraZeneca group of companies

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First line simplified FOLFOXIRI in metastatic colorectal cancer (MCRC) patients (pts): results of a phase II study.

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Background: In our previous phase I-II study (Falcone et al, J Clin Oncol 2002) first line FOLFOXIRI (CPT-11 125-175 mg/sqm 1h IV infusion on day (d) 1, oxaliplatin (LOHP) 100 mg/sqm 2h IV infusion on d1, l-LV 200 mg/sqm 2h IV infusion on d1, 5-FU 3800 mg/sqm 48-h IV chronomodulated continuous infusion starting on d1, repeated every 2 weeks) demonstrated high antitumor activity (ORR=71.4%) and promising efficacy (median PFS=10.4 months and median OS=26.5 months) in MCRC. However this regimen required a chronomodulated infusion of 5-FU and because of neutropenia 60% of pts received G-CSF and delivered dose intensity was approximately only 78% of planned. Therefore we conducted the present phase II study to evaluate the safety and the activity of a simplified FOLFOXIRI regimen which could be more easily feasible in a multicenter setting.

Patients and methods: A total of 32 pts with unresectable MCRC received CPT-11 165 mg/sqm d 1, LOHP 85 mg/sqm d1, l-LV 200 mg/sqm d1, 5-FU 3200 mg/sqm 48-h continuous infusion starting on d1, repeated every 2 weeks: median age was 63 yrs (43-74), ECOG performance status was e 1 in 14 (44%) pts, 17 (53%) pts had multiple metastatic sites and 9 (28%) were pretreated with 5-FU or raltitrexed.

Results: All 32 pts were evaluated for safety and more relevant toxicities were: grade 4 neutropenia (34%), febrile neutropenia (3%), grade 3 thrombocytopenia (3%), grade 3 diarrhea (16%), grade 3 stomatitis (6%) and grade 3 peripheral neurotoxicity (3%); no toxic deaths occurred. Intention to treat analysis for activity showed 4 CR, 19 PR, 5 MR, 2 SD and 2 PD for an overall response rate (CR+PR) of 72% (95%CI: 53-86%). Median duration of responses was 10.5+ months; 7 (22%) pts with residual liver or lung metastases were radically resected after chemotherapy. After a median follow up of 13.4 months median PFS was 10.8 months and median survival has not yet been reached.

Conclusions: This simplified FOLFOXIRI combination has manageable toxicities and significant antitumor activity in MCRC pts. Therefore the Gruppo Oncologico Nord Ovest (GONO) has started a randomized multicenter phase III study comparing this regimen to standard FOLFIRI.

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A study of capecitabine in elderly patients as first line treatment in advanced or metastatic colorectal cancer

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Background: Determine the efficacy and toxicity profile of a twice daily oral capecitabine administration at 2500 mg/m²/day as first line in elderly patients with advanced or metastatic colorectal cancer.

Material and methods: Patients aged ≥70 years with advanced or metastatic colorectal cancer (CRC) histologically confirmed, who had not received prior chemotherapy, at least 1 measurable lesion (RECIST), ECOG ≤ 2 and bone marrow, renal and hepatic function adequate, were eligible for this open label study. Patients were treated with oral capecitabine at 2500 mg/m²/day 2 weeks in a 3 weeks course. This scheme was repeated in 8 cycles. This dose of capecitabine should be reduced, as established in the protocol, to capecitabine 1875 mg/m²/day when toxicity grade II-III occurred. Toxicity was evaluated every cycle using WHO toxicity criteria.

Results: 51 patients (pts) have been included in this analysis (M/F 31/20), median age 75 years old (71-90). ECOG 0:14(27.5%), 1:30(58.8%), 2:7(13.7%). 81.6% had not comorbidity, 78.3% had mild independence from any help (Barthel Index) and most of them (M/F 60.7%/44.4%) were autonomous (Lawton Index). Median of metastatic locations was 1 (62.5% with 1 location and 37.5% with 2 location or more) located mainly in liver (66.7%) and lung (33.3%). Up to date 50 pts received a total of 223 cycles (median 4, range 1-8), median relative dose intensity of 0.88. All these pts were evaluated for safety analysis. Grade III/IV toxicities per pt included thrombocytopenia(4%), leucopenia(2%), neutropenia(2%), diarrhea(6%), asthenia(6%), dyspnea(6%), nausea(2%), vomiting(2%), epigastric pain(2%), liver(2%), renal(2%), hand-foot syndrome(2%), anorexia(2%), abdominal pain(1%), thoracic pain(1%), and hyperglycemia(1%). There was not any significant differences in grade III/IV toxicities between the general population and the population over 80 years of age. Efficacy: To date 10 pts were not evaluable for response: 5 early withdraw (2 due to toxicity and 3 exitus), 3 dropped-out without efficacy evaluation and 2 are still undergoing treatment. 40 pts were evaluable for efficacy, 1 achieved CR, 9 PR, 22 SD and 8 PD resulting in an ORR of 25% (CI 95%: 11.6-38.4%). Median time to progression was 7.9 months. Nine pts (28.1%) obtained clinical benefit during treatment.

Conclusion: Twice daily oral capecitabine in elderly patients seems to be a well tolerated first line treatment in patients with advanced or metastatic CRC.

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Optimal dosing schedule for combination therapy with capecitabine and irinotecan in a human colorectal cancer (CRC) xenograft model

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Background: Capecitabine (Xeloda®) and irinotecan (CPT-11) are highly active single agents for the treatment of advanced/metastatic CRC. Recently, several clinical studies of capecitabine/irinotecan combinations have been performed in the EU and US, and high antitumor activity has been demonstrated. However, neutropenia and diarrhea have been reported to be dose-limiting toxicities of the combination, and a modality to reduce these adverse effects would be helpful. The present study was conducted to establish an optimal schedule of the combination in murine models that maintains potent antitumor activity but shows no increase in diarrhea.

Methods: Gastrointestinal toxicity in mice was estimated by observing the feces and by detecting occult blood in the feces using an occult blood testing kit (Shionogi). Antitumor efficacy was evaluated in a human colon cancer COLO205 xenograft model.

Results: We first used a murine model to examine the dosing regimen of single-agent irinotean, which is capable of inducing delayed-type gastroin-