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UFT/LV combined with oxaliplatin (TEGAFOX) or with irinotecan (TEGAFIRI) as first-line treatment for metastatic colorectal cancer patients (pts). Results of a randomized phase II I.T.M.O. study

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Background: Even if the combined therapies (FOLFIRI and FOLFOX) represent the first line approach in MCRC, the oral fluoropirimidines (UFT) and leucovorin (LV) have demonstrated comparable efficacy to bolus fluorouracil and LV, with clinically safety advantages. The aim of this multicenter trial was to evaluate the efficacy (objective response rate) and safety profile (onset of grade 3–4 side effects) of TEGAFOX or TEGAFIRI, considering the results of the corresponding infusional regimens. The study was designed according to the methods proposed by Thall, Simon and Estey.
Material and Methods: 143 pts with measurable, and unresectable metastatic colorectal cancer were randomized to receive: TEGAFOX (UFT 250 mg/m^2/day d1–14, LV 90 mg/day d1–14, oxaliplatin 120 mg/m^2/d 1; q21) or TEGAFIRI (UFT 250 mg/m^2/day d1–14, LV 90 mg/day d1–14, irinotecan 240 mg/m^2/d 1; q21). The pts with hepatic metastases could undergo surgery after documented objective remission.
Results: 69 pts were assigned to TEGAFIRI and 74 cases to TEGAFOX treatment. Characteristics were well balanced between the two arms. TEGAFIRI: median age 61yrs (range 36–74); PS: 0/1(%):85/15; colon 70%, rectum 30%; pts with more than one metastatic site: 53%; prior adjuvant therapy:19%; metastatic disease at first diagnosis: 72%. TEGAFOX: median age 62 yrs (range 23–73); PS: 0/1/2(%):90/7/3; colon 73%, rectum 27%; pts with more than one metastatic site: 41%; prior adjuvant therapy:19%; metastatic disease at first diagnosis: 67%. The median number of administered cycles was: 6 (3–8). Preliminary safety and efficacy analysis as follows:

	TEGAFIRI	TEGAFOX
Safety n. evaluable pts	*68*	*73*
G3/4: any type	37%	21%
Neutropenia	12%	1%
Diarrhea	16%	4%
Vomiting/Nausea	10%	3%
Neurotoxicity	–	5%
Efficacy n. evaluable pts	*53*	*68*
PR	35%	32%
CR	11%	9%

Definitive data on safety and efficacy (including pts who underwent liver resection after objective remission) will be presented.
Conclusions: Both TEGAFIRI and TEGAFOX represent an effective and tolerable first-line therapy in MCRC pts. The TEGAFOX safety profile seems to be comparable to equivalent infusional regimen, and supports its use in elderly pts. The interesting response rate obtained with TEGAFIRI makes this regimen suitable for further evaluation in the neoadjuvant setting.
Data management by I.T.M.O. (Italian Trials in Medical Oncology) Scientific Service.

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Pathological complete response following preoperative chemoradiation in rectal cancer: An updated analysis of phase II/III trials

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Background: Pathological complete response (pCR) has been used as a surrogate marker of the efficacy of chemoradiation schedules in rectal cancer. In the absence of completed randomised studies, comparison of pCR rates in prospective studies although hindered by confounding factors may help to generate hypotheses for future trial design.
Method: Prospective phase II and chemoradiation arms of phase III trials reported up to May 2005 were included if they defined the following minimum variables: drugs employed during chemoradiation, radiation dose and pCR rate. A multivariate analysis was performed to examine the effect on the pCR rate of the above variables and in addition, the use of neoadjuvant chemotherapy, the type of publication (peer reviewed vs. abstract) and whether the tumours were stated to be inoperable, fixed or threatening the circumferential resection margin. The method of analysis was weighted linear modelling of the pCR rate which was normalised by the arcsine transformation.
Results: 48 phase II and 8 phase III trials were identified in which a total of 3760 patients received chemoradiation. Statistically significant factors associated with pCR were the use of two drugs ($p = 0.001$), the method of anti-metabolite administration ($p = 0.02$) and radiotherapy dose ($p = 0.02$). The administration of a two drug regime or the use of continuous infusion 5-flurouracil appeared to be associated with higher rates of pCR whereas lower rates of pCR appear to be associated with doses of radiotherapy <45 Gray (Gy). There was no evidence of a radiotherapy dose response above 45 Gy.
Conclusions: The use of a two drug regime, the mode of delivery and type of antimetabolite and radiotherapy doses of 45 Gy or more appear to be related to the incidence of pCR following chemoradiation for rectal cancer. Important factors not considered in this analysis include variability in staging investigations, pathological examination and the delay between chemoradiation and surgery. In addition the toxicity of two drug chemoradiation schedules requires adequate investigation.

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Starting bevacizumab shortly after venous access device implantation appears not to increase wound healing/bleeding complications nor catheter related thromboses – preliminary results from First BEAT

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Background: In a phase III pivotal trial in patients (pts) with metastatic colorectal cancer (mCRC), bevacizumab (BEV, Avastin®) increased overall survival by 30% when added to first-line IFL chemotherapy (CT). First BEAT evaluates the safety of BEV in a broader pt population with mCRC using a variety of CT regimens. Pts with major surgery within 28 days of first BEV dose are excluded from clinical trials. We report here the outcome of minor surgery such as venous access device (VAD) implantation. VADs in cancer pt are associated with a 4–6% risk of catheter related thrombosis (CRT) in the affected vein.
Material and methods: Up to 2000 eligible pts starting with first-line mCRC CT will be treated until progression with BEV (5 mg/kg every 2 weeks [5FU based CT] or 7.5 mg/kg every 3 weeks [Capecitabine based CT]). Formal protocol visits are scheduled every 3 months, followed by a final visit 30 days after the last BEV dose. At these visits all wound healing (any) and bleeding complications (at VAD), as well as CRT are assessed (CTCAE, v3.0).
Results: By May 17, 2005, 606/951 pts (male 58%; median age 60 years [31% were >65 years]; PS 0–1 99%) had data available for baseline analyses. 286/606 (47%) pts had a VAD implanted including 215 (36%) with an indwelling venous catheter and 47 (8%) with a peripheral catheter. CT regimens used with BEV included FOLFOX (47%) and FOLFIRI (27%). 80 (13%) pts had their VAD placed 7 days prior to first BEV dose, and 36 (6%) pts 2 days prior to first BEV dose. 39/286 (14%) pts received anticoagulants/antiplatelet therapy (8% low dose aspirin, 2% warfarin, 3% LMW heparin, <1% unfractioned heparin, <1% other), which was stopped in 10 pts prior to BEV initiation.
118/286 pts have follow up data. Wound healing complications were reported for 3 (2.5%) pts (all CTC AE grade 1; none in pts with VAD implantation within 7 days). No bleeding at VAD wound was reported. CRT was reported in 3 (2.5%) pts (1 CTC AE grade 2, 2 CTC AE grade 3; all in pts with VAD implantation within 7 days).
Follow-up of >300 pts is expected to be available by October 2005.
Conclusions: BEV treatment in combination with continuous infusion CT appears safe. CRT and bleeding at insertion site of VAD were not increased in this series. The implantation of VAD shortly before starting BEV treatment did not result in an increased risk of wound healing complications. The addition of BEV should not lead to delays in starting treatment after implantation of VAD.