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Safety and efficacy of bevacizumab (BEV) and chemotherapy in elderly patients with metastatic colorectal cancer (mCRC): results from the BEAT observational cohort study

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Background: Addition of BEV to chemotherapy prolongs overall survival (OS) and progression-free survival (PFS) in 1st- and 2nd-line treatment of patients with mCRC. Subgroup analyses from a recent pooled analysis of BEV pivotal studies [Kabbinavar et al, JCO 2009] have shown that older (⩾65 years) and younger (<65 years) patients derive similar PFS and OS without a difference in the risk–benefit profile. We evaluated the safety and efficacy of BEV + chemotherapy by age group in patients who participated in BEAT (Bevacizumab Expanded Access Trial; study ID MO18024).
Methods: Patients with unresectable mCRC received physician's choice of chemotherapy plus bevacizumab (5 mg/kg q2w [5-FU regimens] or 7.5 mg/kg q3w [capecitabine regimens]). The primary endpoint was safety. Secondary objectives were progression-free survival (PFS) and overall survival (OS). BEAT is now complete. The effect of age on adverse events (AEs) of interest for BEV was analysed in patients aged <65, 65−74, and ⩾75 years. The effect of age on survival was assessed using a Cox regression.
Results: Of the 1914 patients enrolled in BEAT, half received BEV + oxaliplatin-based therapy (FOLFOX, bFOL, XELOX, other), 35% received BEV + irinotecan-based therapy (FOLFIRI, IFL, XELIRI) and the remainder received BEV + monotherapy (5-FU bolus, 5-FU infusion, capecitabine). 1286 (67%) patients were <65 years, 499 (26%) were 65−74 years and 129 (7%) were ⩾75 years. Median PFS and OS appear to be similar for the <65 and 65−74 age categories (Table). Median OS was numerically lower in the ⩾75 year group, probably due to the small number of patients included in this category. BEV-targeted safety was similar in those aged <65, 65−74 and ⩾75 years (Table).
Conclusions: These results show that older patients with mCRC can derive similar benefit from BEV + chemotherapy as younger patients without a substantial increase in toxicity and suggest that age alone should not preclude effective treatment.

	Age group, years			
	All (n = 1914)	<65 (n = 1286)	65−74 (n = 499)	⩾75 (n = 129)
Survival, months				
Median PFS	10.8	10.8	11.2	10.0
Median OS	22.7	23.5	22.8	16.6
Safety, n (%)				
Gastrointestinal perforation	37 (1.9)	22 (1.7)	11 (2.2)	4 (3.1)
Arterial thromboembolism	29 (1.5)	14 (1.1)	10 (2.0)	5 (3.9)
Grade 3/4 bleeding	44 (2.3)	33 (2.6)	9 (1.8)	2 (1.6)
New/worsening hypertension	572 (29.9)	354 (27.5)	180 (36.1)	38 (29.5)

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FOLFOX-4 versus FOLFIRI in the treatment of metastatic colorectal cancer – a prospective randomised study

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Background: The choice of chemotherapy protocol for patients with metastatic colorectal carcinoma (mCRC) remains an open discussion. A prospective study was commenced in 2002 in order to analyze differences in terms of overall survival and progression free survival for patients with mCRC treated with FOLFOX-4 and FOLFIRI, respectively.
Methods: The study was conducted in the Oncology Clinic of Craiova, Romania during May 2002 – November 2008. The most important eligibility criteria were: mCRC, +/− past adjuvant chemotherapy, measurable disease, no liver, renal or other severe organic impairment, ECOG performance status 0 or 1. Patients were randomized 1:1 (using a simple randomization software) in 2 groups: A, receiving the standard FOLFOX-4 regimen (oxaliplatin 85 mg/sqm, folinic acid 200 mg/sqm, 5-fluorouracil 400 mg/sqm bolus iv and 5-fluorouracil 600 mg/sqm continuous iv infusion for 22 hours, every 14 days); B, comprising patients who received standard FOLFIRI regimen (irinotecan 180 mg/sqm, folinic acid 200 mg/sqm, 5-fluorouracil 400 mg/sqm bolus iv and 5-fluorouracil 2400 mg/sqm continuous iv infusion for 46 hours, every 14 days). The treatment was discontinued due to intolerable toxicity or disease progression. Stratification criteria were: sex, age, past adjuvant chemotherapy or not, presence of complications at diagnosis. The endpoints of the study were: median overall survival, disease progression free survival and quality of life in each group. Kaplan Meier curves were used for statistical analysis – for overall survival and the logrank test.
Results: 356 patients admitted between May 2002 and November 2003 were randomized: 180 in group A and 176 in group B. The median number of chemotherapy cycles administrated was 9.4 in group A and 9.2 in group B. No significant difference between median overall survival appeared between the 2 groups: 17.8 months in group A and 17.2 months in group B, with a hazard ratio for survival of 0.88 (95%CI, 0.75−1.12, $p < 0.004$). Progression free survival was also not significant different between these 2 groups: 6.9 months for group A and 7.2 months for group B. No significant difference was observed in term of quality of life between the groups.
Conclusions: First line chemotherapy regimen associated with molecular target therapy in metastatic colorectal cancer remains a decision of the physician, as no significant differences were observed between FOLFOX-4 and FOLFIRI regimens.

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Influence of Cetuximab applied as biweekly infusion on the plasma disposition of CPT 11 and its metabolites in advanced colorectal cancer

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Background: Combination of the Anti EGFR monoclonol antibody Cetuximab (C-MAB) with Irinotecan (CPT 11) is clinically effective in pretreated advanced colorectal cancer (ACRC) pts. As a more convenient alternative a biweekly instead of standard weekly C-MAB was introduced in clinical trials based on pharmakokinetic (PK) data demonstrating no difference between the respective C-MAB schedules (Pfeiffer et al., Tabernaro et al). Complex metabolism of CPT 11 using different enzymatic pathways makes this drug a target for potential PK interactions. Therefore, using biweekly C-MAB combined with FOLFIRI schedule, impact of C-MAB on the PK profile of CPT11 and its metabolites was investigated.
Methods: 11 pretreated ACRC pts received C-MAB as a 2H infusion of 500 mg/m^2 immediately followed by CPT11 180 mg/m^2 1 HR infusion combined with infusional 5-FU folinic acid (FOLFIRI). For monitoring the conc of CTP11 and metabolites plasma samples were collected at 13 timepoints over 48H (quantation bei HPLC). The study was performed as a paired cross over with intrapatient comparison: baseline analysis of CPT 11 on d1 of cycle 1 with the first C-MAB infused on d3 at end of sampling period of 48H. During all following cycles C-MAB was infused immediately before CPT11 and PK-analysis repeated on d1 of cycle 3 or 4 (PK assessment by Win nonlin pro v5.0).
Results: No influence of C-MAB on the PK of CPT11 and the main active metabolite SN38 was documented: AUC Ratio of CPT11 vs SN38 was 40 (mono) and 38.8 (comb), and AUC of SN38 represented 2.4% of