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Meeting Abstract: 2014 Gastrointestinal Cancers Symposium

FREE ACCESS Cancers of the Colon and Rectum January 20, 2014

# A UGT1A1 genotype-guided dosing study of irinotecan in metastatic colorectal cancer (mCRC) patients (pts) treated with FOLFIRI plus bevacizumab (BEV).

**Authors**: Manish Sharma, Giuseppe Toffoli, Angela Buonadonna, Elena Marangon, Blase N. Polite, Sergio Frustaci, and Federico Innocenti | AUTHORS INFO & AFFILIATIONS

**Publication**: Journal of Clinical Oncology Volume 32, Number 3_suppl https://doi.org/10.1200/jco.2014.32.3_suppl.562

## Abstract

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**Background:** Dosing based on UGT1A1*28 genotyping has been demonstrated to reduce irinotecan-related adverse events. Previous data (Toffoli et al. JCO, 2010) showed that mCRC pts treated with first-line FOLFIRI tolerated higher doses (310 mg/m$^2$ for *1/*28; 370 mg/m$^2$ for *1/*1) of irinotecan than the standard 180 mg/m$^2$. The aims of this study (NCT01183494; supported by Eudract 2009-012227-28) were to define the maximally-tolerated dose (MTD) of irinotecan in FOLFIRI plus BEV as first-line therapy in mCRC pts and to determine whether BEV alters irinotecan pharmacokinetics (PK). **Methods:** Pts were accrued at 3 sites: Chicago (USA), Aviano (Italy), Rome (Italy). In *1/*28 and *1/*1 pts (*28/*28 pts were excluded), irinotecan was administered at an initial dose of 260 mg/m$^2$ IV every 2 weeks. The dose was escalated to 310 and 370 mg/m$^2$ if 0/3, <2/6, or <3/10 pts had a DLT (grade 3-4 non-hematologic or grade 4 hematologic toxicity during the first 28-day cycle). MTD was defined as the highest dose at which <4/10 pts had a DLT. 5-FU was administered as a 400 mg/m$^2$ IV bolus followed by 2400 mg/m$^2$ IV over 46 hours, plus 200 mg/m$^2$leucovorin. BEV was administered at 5 mg/kg IV on day 3 (2 days after irinotecan) and on day 15 (before irinotecan), then every 2 weeks. Irinotecan PK were collected on days 1-3 (in absence of BEV) and on days 15-17 (in presence of BEV). **Results:** 44 pts (23 *1/*28; 21 *1/*1) were enrolled and 43 were evaluable for DLTs during cycle 1 (Table). Neutropenia and diarrhea were the most common DLTs and were each observed in 5 of 11 (45%) pts with DLTs. The MTD is 260 mg/m$^2$ in the *1/*28 cohort and at least 310 mg/m$^2$in the *1/*1 cohort. In a preliminary analysis of 22 pts, BEV decreased the AUC of SN-38, the active metabolite of irinotecan (p = 0.026 by Wilcoxon matched pairs signed rank test). **Conclusions:** In first-line therapy of mCRC with FOLFIRI plus BEV, irinotecan doses higher than the standard dose can be safely administered based on UGT1A1 genotype. The impact of this genotype-guided dosing approach on survival will be established in future trials. Clinical trial information: NCT01183494.

| | # DLTs / # pts, according to irinotecan dose | | |
|---|---|---|---|
| UGT1A1 genotype | 260 mg/m$^2$ | 310 mg/m$^2$ | 370 mg/m$^2$ |
| *1/*1 | 1/10 | 2/10 | Accrual ongoing |
| *1/*28 | 2/10 | 4/10 | 2/3 |

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