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A multicenter phase II study of personalized FOLFIRI-cetuximab for safe dose intensification

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ABSTRACT

We conducted a multicenter proof of concept phase II trial in patients with advanced colorectal cancer receiving FOLFIRI-cetuximab regimens to explore individual drug tailoring using pharmacogenetics and pharmacokinetics (PK) monitoring. Patients were stratified by their pharmacogenetic/phenotypic status: the irinotecan dose was adjusted according to the number of TA tandem repeats in the UGT1A1 promoter, while the 5-fluorouracil (5-FU) dose was initially adjusted according to dihydropyrimidine dehydrogenase (DPD) activity at initial screening (5-FU$^{ODPM\ Tox}$) followed by PK-guided dose optimization (5-FU$^{ODPM\ Protocol}$). An advanced cetuximab PK/pharmacodynamics (PD) study was performed but dosage remained unchanged. Eighty-five patients receiving second-line chemotherapy were enrolled. Mean irinotecan doses at 3 months were 247 ± 50, 210 ± 53 and 140 ± 21 mg/m^2 for those with 6/6 (33), 6/7 (26), and 7/7 (7) TATA repeats in the UGT1A1 promoter region, respectively. The 5-FU dose was initially reduced in four patients with DPD deficiency, but mean 5-FU dose at 3 months was 2,412 ± 364 mg/m^2 (1,615–3,170 mg/m^2). Grade 4 toxicities were not encountered and grade 4 neutropenia occurred in 6.8%, 5.9%, and 0% of patients with 6/6, 6/7, and 7/7 UGT1A1 genotypes. The objective response rate was 25.8% among the 85 patients, 57.3% in patients with tumors wild type (WT) for KRAS, and 25% in those whose tumor harbored a mutant-KRAS. Secondary resection of hepatic metastases was performed in 31.7% of patients. Median progression-free survival (PFS) for all 85 patients was 181 days and 200, 132, and 121 days for patients with 6/6, 6/7, and 7/7 UGT1A1 genotypes, respectively; these differences were not statistically different. In parallel, a strong relationship was shown between cetuximab AUC and regimen efficacy. We conclude that personalized drug tailoring when administering in FOLFIRI + cetuximab allows for safe and efficient individual dose intensification.

1. Introduction

In metastatic colorectal cancer (mCRC), resection of liver/lung metastases is currently the most effective approach to achieve prolonged progression-free (PFS) and overall survival (OS) and the only potentially curative intervention [1,2]. However, many patients present with metastases initially deemed unresectable, and in this case first-line chemotherapy may produce sufficient tumor shrinkage to allow for a complete resection [3,4]. In order to enhance the efficacy of conventional regimens such as FOLFOX and FOLFIRI, whose impact on the R0–R1 resection rate is disappointing, different approaches have been explored (Table 1). High response rates accompanied by promising resection rates have been achieved using tritherapy, either FOLFIRINOX or FOLFOXIRI, but both regimens have been associated with higher toxicities [5–7]. For example, in a randomized study in

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Table 1
Assessment of tritherapies, combining 5-FU, irinotecan, and oxaliplatin, and comparison with conventional biotherapies.

METHEP trial: Comparison of 3 intensified chemotherapy regimens in first-line treatment of CRC patients with initially unresectable or not optimally resectable liver metastases.	Randomized phase II trial. Objective: to evaluate neoadjuvant intensified chemotherapy in potentially resectable or unresectable liver metastases from CRC. Standard therapy (FOLFIRI/FOLFOX4) or intensified chemotherapy (FOLFIRI-HD / FOLFOX7 / FOLFIRINOX). Primary endpoint: ORR. Secondary endpoints: R0 surgical resection, best ORR, PFS, and OS.	122 patients received FOLFIRI + FOLFOX4 / FOLFIRIHD / FOLFOX7 / FOLFIRINOX: • %G3/4 neutropenia: 24 / 19 / 10 / 23 • %G3/4 diarrhea: 0 / 6 / 3 / 23 • %G3/4 mucositis: 0 / 3 / 0 / 7 • %ORR after first 4 cycles: 33 / 47 / 43 / 57 FOLFIRINOX: • Best conversion rate to resectability (67%) • R0, R1: 54/64 patients • Median PFS: 11.9 *v* 9.2 months ($P = .115$) • Median OS 33.4 *v* 17.7 months ($P = .297$) Conclusion: FOLFIRINOX showed promising activity compared with standard or intensified bi-chemotherapy regimens.	Ychou et al, 2013 [5]
Randomized study comparing FOLFOXIRI + bevacizumab with FOLFIRI + bevacizumab in first-line mCRC patients	Phase III randomized study of patients with unresectable mCRC recruited from 34 Italian oncology units. 508 patients randomly assigned (1:1) to receive FOLFIRI + bevacizumab or FOLFOXIRI + bevacizumab	FOLFOXIRI *v* FOLFIRI: • ORR: 65% *v* 53% ($P = .006$) • Median PFS: 12.1 *v* 9.7 months ($P = .003$) • Median OS: 31.0 *v* 25.8 months ($P = .054$) • Toxicity significantly higher in the FOLFOXIRI group: G3/4 neutropenia (50%); febrile neutropenia (8.8%); stomatitis (8.8%); diarrhea (18.8%); and neuropathy (5.2%). Updated data FOLFOXIRI *v* FOLFIRI at median follow-up of 48 · 1 months: • Median OS 29.8 *v* 25.8 months ($P = .03$).	Loupakis et al, 2014 [6] Cremolini et al, 2015 [7]
Efficacy of FOLFOXIRI + bevacizumab in liver-limited mCRC: an analysis of clinical studies by Gruppo Oncologico del Nord Ovest	Assess efficacy of FOLFOXIRI + bevacizumab. Pooled analysis of patients with unresectable and liver-limited mCRC, treated with first-line FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab in three prospective clinical trials by Gruppo Oncologico del Nord Ovest.	205 patients with liver-limited disease selected, out of 541 treated patients. ORR: FOLFOXIRI + bevacizumab (69%) and R0, R1 resection rates: FOLFOXIRI + bevacizumab (36%) R0/R1 resected patients: • Longer median PFS: 18.1 *v* 10.7 months, ($P < .001$) • Longer median OS: 44.3 *v* 24.4 months, ($P < .001$) • 5-year PFS and OS rates in R0 resected patients, 12% and 43% Conclusion: "FOLFOXIRI + bevacizumab demonstrates efficacy in the conversion setting with considerable long-term outcome results"	Cremolini et al, 2016 [7]

mCRC = metastatic colorectal cancer; G = toxicity grade; ORR = objective response rate; PFS = progression-free survival; OS = overall survival; 5-FU = 5-Fluorouracil; FOLFOX = 5-FU + leucovorin + oxaliplatin; FOLFIRI = 5-FU + leucovorin + irinotecan; FOLFIRINOX = 5-FU + leucovorin + irinotecan + oxaliplatin.

potentially resectable or unresectable liver metastases, patients were randomized to either standard (FOLFIRI/FOLFOX4) or intensified bitherapy (FOLFIRI-HD/FOLFOX7) or tritherapy (FOLFIRINOX) [5]. A total of 122 patients were treated. Intensified bitherapy and tritherapy led to greater efficacy with FOLFIRINOX achieving the best objective response rate (ORR) (57%), the best conversion rate to resectability (53.3% R0/R1), and longer PFS (11.9 months) and OS (33.4 months). However, this regimen induced significantly higher morbidity rates, and higher rates of grade 3/4 neutropenia, thrombocytopenia, diarrhea, mucositis, and neuropathy. In a separate randomized study, 508 patients were randomly assigned to receive FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab (Table 1). The tritherapy FOLFOXIRI in combination with bevacizumab achieved higher ORRs (65 *v* 53%, $P = .006$) and longer median PFS values (12.1 *v* 9.7 months; $P = .003$). FOLFOXIRI plus bevacizumab also demonstrated greater efficacy in the conversion setting with considerable long-term outcome results but at the cost of significantly higher grade 3/4 neutropenia (50%), febrile neutropenia (8.8%), stomatitis (8.8%), diarrhea (18.8%), and neuropathy (5.2%). More recently, Gruppo Oncologico del Nord Ovest has reported a pooled analysis of clinical studies assessing the efficacy of FOLFOXIRI plus bevacizumab compared to FOLFIRI plus bevacizumab in liver-limited mCRC patients. FOLFOXIRI plus bevacizumab achieved a higher ORR (69%) and R0/R1 resection rates (36%) with patients in whom an R0/R1 resection was possible having a significantly longer median PFS (18.1 *v* 10.7 months, hazards ratio [HR]: 0.48 [0.35–0.66], $P < .001$). Toxicity has not been reported.

Despite the foregoing, it remains unclear whether three active cytotoxic agents should be employed in this indication given the enhanced ORR and resection rates are accompanied by a much higher frequency and severity of toxic events. Other regimens used in first line including cetuximab with either FOLFOX6 or FOLFIRI and high-dose irinotecan have been explored and reported to achieve ORRs as high as 62% with cetuximab and a better 34% R0 resection, equivalent to the data obtained with tritherapy [8–12]. However, these data still remain insufficient, struggling to a compromise between safety and efficacy, and thus clearly complementary approaches are needed.

Several studies have reported wide inter-individual variability of both 5-fluorouracil (5-FU) and irinotecan (CPT-11) in terms of plasma

Table 2
5-FU plasma clearance displays wide interpatient variability and BSA-based 5-FU dosing leads to significant under- or over-dosing.

Comparison of conventional 5-FU dosing *v* PK-guided 5-FU dose adjustment in terms of response, tolerability, and survival	Phase III, multicenter, randomized study: 208 mCRC patients in 2 groups, with target AUC 20–25 mg h/L in PK-guided group.	• ≈ 70% required dose adjustment to achieve optimal therapeutic dose (target AUC): > 58% dose increased; 10% dose reduction. • 8% of patients with BSA dosing had AUC within optimal range. • PK-guided 5-FU dose: Higher CR/PR rates (39% *v* 19%; $P = .0004$) and median OS: (22 *v* 16 mo; $P = .08$). • BSA dosing: more toxic events in ($P = .003$).	Gamelin et al, 2008 [13]
Review of PK-guided dose adjustment of 5-FU	Review of PK-guided 5-FU dosing. Discussed potential of this approach to advance therapeutic outcomes	• Only 20–30% of patients treated with appropriate dose for optimal plasma concentration; 40–60% under-dosed; 10–20% over-dosed. • Studies have shown PK-guided dosing substantially improves safety and efficacy.	Saif et al, 2009 [4]
BSA-based dosing of 5-FU results in extensive interindividual variability in patients on FOLFOX regimens	357 sequential patients receiving 5-FU 2,400 mg/m^2 (FOLFIRI/FOLFOX6 ± bevacizumab)	• Wide range of AUC (1-69 mg · h/L); mean AUC of 20.4 mg · h/L. • Only 21.3% achieved target 5-FU concentrations (AUC 20-24 mg · h/L); 51% below range, with 23.6% well below range with AUC ≤ 14 mg · h/L; 27.7% over target range. • Similar distribution of AUCs whether FOLFOX or FOLFIRI or ± bevacizumab	Saam et al, 2011 [14]
Individual 5-FU dose adjustment in FOLFOX based on PK follow-up compared with conventional BSA-dosing	Phase II, proof-of-concept study in first line mCRC. 118 had individually determined PK-adjusted 5-FU; 39 treated with BSA-based 5-FU dosing	• Wide range of 5-FU plasma clearance: 59.82-245.73 L · m^{-2} · h^{-1}); mean: 130.59 ± 38.35 L · m^{-2} · h^{-1}. • Wide range therapeutic optimal dosage compared to 2,500 mg/m^2: mean 110 ± 21.7%. • 5-FU dose increased ≥ 10% in 75 (63.5%) with mean increase 20 ± 8% (range, 10–40%). Dose increased > 20% in 42 (36%), with mean increase 26 ± 6% (range, 20–40%). 5-FU dose decreased ≥ 10% in 22 (18.6%) patients, with mean decrease 20 ± 9% (range, 10–40%). Dose decreased > 20% in 14 (12%), with mean decrease 26 ± 5.9% (range, 20–40%). • In BSA-based dosing, 5-FU dose was early reduced in 4 patients, 15 ± 4% (range, 10–25%), because of G3 toxicity.	Capitain et al, 2012 [15]
Modeling the 5-FU AUC *v* dose relationship to develop a PK dosing algorithm for CRC patients receiving FOLFOX6	589 patients receiving FOLFOX6 regimen. Subset who had at least two consecutive cycles tested, received 1,600–3,600 mg/m^2 5-FU, and had a blood sample collected after ≥ 18 hours, was used to conduct regression modeling of the AUC change versus dose change	• Dose changes in the range of 291–727 mg/m^2 sufficient to adjust the AUC to a potential therapeutic threshold of > 20 mg · h/L for most patients. • AUC values below threshold have higher risk for under-dosing, with lesser efficacy. • Assuming 2,400 mg/m^2 baseline dose, a maximum 727 mg/m^2 dose increase would correspond to a 30% increase and are needed by patients with initial AUC ≤ 10 mg h/L.	Kaldate et al, 2012 [16]

5-FU = 5-fluorouracil; AUC = area under the curve; BSA = body surface area; CR = complete response; PR = partial response; mCRC = metastatic colorectal cancer.

clearance and AUC when administered based on body surface area (BSA) (Tables 2 and 3). BSA is not a clear significant covariate and does not resolve this wide pharmacokinetics (PK) variability. Moreover, for both drugs, a dose-effect has been reported suggesting that a higher drug dose may be optimal. The 5-FU dose administered with the most commonly used regimens—LV5FU2, FOLFOX, and FOLFIRI—is still based on BSA, 2,400 mg/m^2 intravenously (IV) 48-hour infusion, and represents a compromise between efficacy and toxicity, but it has been shown in several consistent studies to lead to either under- or over-dosing in about 70% of the patients, with under-dosing a more common outcome (Table 2).

Likewise, the dose of irinotecan is based on BSA, although a flat dose would be adequate with the recommended dose of irinotecan explored both as monotherapy and in combination with 5-FU (Tables 4 and 5). While the conventional irinotecan dose in the FOLFIRI regimen is 180 mg/m^2, higher doses, up to 260 mg/m^2, have achieved greater efficacy but at the expense of higher toxicity (Table 5). In patients with unresectable mCRC, a regimen of 260 mg/m^2 irinotecan plus LV5FU2 allowed 28% of patients to undergo a second surgery with curative intent, although 45% of patients required granulocyte colony-stimulating factor (G-CSF) support [20,21]. Additionally, cetuximab dose intensity has been explored in a randomized study that showed greater efficacy but again at the expense of more toxicity [21].

Exposure to both irinotecan and 5-FU can vary greatly as a result of individual patient differences in the activities of various enzymes, especially UDP-glucuronosyl transferase (UGT) and dihydropyrimidine dehydrogenase (DPD) [29–31]. Thus it is not surprising that commonly used BSA dosing can lead to over-dosing in patients with low metabolism and under-dosing in those with accelerated metabolism [32,33]. Individual dosing of cytotoxic drugs based on pretreatment genotyping/phenotyping and PK monitoring during treatment offers an alternative approach. The most common polymorphism of the *UGT1A1* gene in Western populations involves different numbers of TATA box repeats, from 5 to 7, in the promoter of UGT1A1. Differences in the levels of

Table 3
Irinotecan plasma clearance displays a wide interpatient variability and BSA-based 5-FU dosing leads to significant either under- or over-dosing.

Impact of body-size measures on irinotecan clearance	50 men, 32 women; median age, 54 years receiving 175 to 350 mg/m^2 irinotecan as 90-min IV infusion	• Mean irinotecan clearance 33.6 ± 10.8 L/h • Interindividual variability 32.1%, unchanged when BSA-adjusted clearance. In a multiple linear regression analysis, BSA, lean body mass, ideal body weight, and BMI were not significant covariate. • BSA not a predictor of irinotecan clearance and SN38 PK and does not contribute to reducing kinetic variability. • Need for a comparative study between irinotecan BSA-based and flat or fixed dosing.	Mathijjsen et al, 2002 [17]
Influence on PK/PD variability of flat-fixed irinotecan dosing	26 cancer patients (12 females) received either 350 mg/m^2 or a fixed dose of 600 mg irinotecan every 3 weeks.	No significant difference between the 2 irinotecan dose groups: • Wide clearance inter-individual variability (25.9 vs 25.1%; $P = .93$) • Similar conversion to SN-38 (47.8 *v* 42.7%; $P = .24$) • Similar SN-38 glucuronidation (71.2 *v* 72.4%; $P = .95$). • Hematological AEs similar ($P > .14$). Conclusion: Flat-fixed dosing of irinotecan does not result in increased PK/PD variability and could supplant BSA dosing	De Jong et al, 2004 [18]
Optimal irinotecan dosing based on factors affecting systemic exposure to SN-38, for personalized irinotecan-based chemotherapy.	Exposure to SN-38, the active metabolite of irinotecan, is characterized by large inter- and intrapatient variability and can cause severe irinotecan-related toxicities	BSA is not a significant predictor of ANC nadir. Flat dosing of irinotecan might be recommended. Conclusion: "Despite these observations, many prescribers and regulators maintain the erroneous belief that a patient with a larger BSA will always require a higher dose to induce the same drug effects".	Fujita et al, 2015 [19]

5-FU = 5-fluorouracil; AUC = area under the curve; BSA = body surface area; BMI = body mass index; AE = adverse events; ANC = absolute neutrophil count.

enzyme activity have been shown to be a function of the number of TATA repeats, a higher number of repeats being associated with lower enzymatic activity. High normal UGT1A1 activity is found in the 45% of the population with six TATA repeats in both *UGT1A1* alleles (6/6); while 10% of the population has seven TATA repeats in both *UGT1A1* alleles (7/7) and has 30% as much UGT1A1 activity (UGT1A1*28 genotype, Gilbert's syndrome). The remaining 45% of the population has UGT1A1 activity intermediate between the 6/6 and 7/7 cohorts and has six TATA repeats in one allele and seven in the other (6/7). In Asian populations, the main relevant polymorphisms are located in the coding region of exon 1 (UGT1A1*6, G71R; a G to A transition at nucleotide 211) [31]. Not surprisingly, several studies have reported close relationships between UGT1A1 genotype and the PK, efficacy, and toxicity of irinotecan [30–32]. Greater irinotecan toxicity has been reported in patients with the 7/7 genotype with lower response rates and shorter PFS values [30,34]. Conversely, patients with the 6/7 and 6/6 genotypes have been able to receive higher irinotecan doses with acceptable toxicity. The latter has led the US Food and Drug Administration to recommend *UGT1A1* genotyping prior to irinotecan administration, but unfortunately this has yet to be widely adopted in clinical practice. Like *UGT1A1*, DPD is subject to genetic polymorphisms and this also results in large variability of 5-FU metabolism with DPD activity following a Gaussian distribution. In a randomized study, individual dose adjustment with PK monitoring has shown increased efficacy without affecting the tolerance [15].

We have previously investigated individual dose adjustments of 5-FU and irinotecan based on pretherapeutic determination of DPD activity through a multiparametric approach and PK monitoring (5-FU$^{\text{ODPM Tox}}$, 5-FU$^{\text{ODPM Protocol}}$, ODPM, Angers, France) and *UGT1A1* genotype [13,29–31,35]. Here we report a phase II study in a population of patients with non-resectable mCRCs receiving second-line chemotherapy using a FOLFIRI + cetuximab protocol. We performed individual dose adjustments so as to safely increase the dose of both irinotecan and 5-FU with a goal of improving efficacy without incurring greater toxicity. Cetuximab PK/pharmacodynamics (PD) was also performed and a correlation between exposure and efficacy was shown and published separately [36].

2. Patients and methods

2.1. Patient samples

Patients from 10 public and private hospitals with measurable pathologically confirmed metastatic adenocarcinoma of the colon or rectum considered for second-line therapy with a FOLFIRI-cetuximab regimen were eligible to participate in this study. The patients had to be > 18 years of age, with measurable metastatic lesions, and have an estimated life expectancy of at least 3 months. The performance status (PS) was evaluated as defined by the World Health Organization (WHO). Written informed consent was obtained from all patients. The study was approved by the Committee on Human-Related Research of Angers and by the local institutional review boards. A computed tomography scan was performed as a baseline. An independent data and safety monitoring committee evaluated all serious adverse events (no. AFSSAP 050832).

Patients were not selected per KRAS mutational status, because this parameter was not officially admitted when the study was conducted. Efficacy per KRAS status has been retrospectively assessed, and is reported herein.

2.2. Treatment

FOLFIRI-cetuximab was administered as follows. Irinotecan was given every 2 weeks, before 5-FU treatment, for 1.5 hours. The initial dose was adjusted according to *UGT1A1* status [1]: 6/6 patients received an initial dose of 210 mg/m² then increased 20%

Table 4
Efficacy and safety assessment of high-dose irinotecan in monotherapy.

Phase I trial administering irinotecan every 3 weeks,	A phase I study to determine MTD, safety, PK, recommended dose with a maximum tolerated dose of 750 mg/m^2	• 64 patients. • At 350 mg/m^2, diarrhea was dose-limiting, but high-dose loperamide allowed dose escalation • With careful monitoring of GI toxicities, a higher dose of 500 mg/m^2 can be recommended.	Abigerges et al, 1995 [22]
High dose-intensity of irinotecan administered every 3 weeks in advanced cancer patients	35 patients included. Primary tumor sites were colon, head and neck, unknown primary, kidney, liver, and others. All had been previously treated. Irinotecan was given at the maximum-tolerated dose (MTD) (600 mg/m^2) or the level below (500 mg/m^2) every 3 weeks	600 mg/m^2 (18 patients): • G3/4 neutropenia, 78% • G3/4 diarrhea, 50% • 1 toxic death 500 mg/m^2 (17 patients): • G3/4 neutropenia, 41% • G3/4 diarrhea: 24% • No toxic deaths 6 ORs in CRC patients previously treated with conventional chemotherapy; 4 in patients who had PD under 5-FU–based chemotherapy.	Merrouche et al, 1997 [23]
Irinotecan dose escalation as CRC first-line therapy	Phase II trial, first course delivered at a dose of 350 mg/m^2 and, in the absence of severe toxicity, following courses delivered at a dose of 500 mg/m^2.	49 patients, 31 (63%) included were able to receive the higher dose with acceptable toxicity. • G3/4 neutropenia: 17% • G3/4 diarrhea: 7% • ORR: 35.5% (24.5% in overall population)	Ychou et al, 2002 [24]
Evaluation of 3 irinotecan treatment regimens	Phase II randomized trial in patients with mCRC as second line after failure of 5-FU or raltitrexed 1. Standard regimen: 350 mg/m^2 irinotecan every 3 weeks 2. Dose escalation starting at 250 mg/m^2 (then 350 and 500 mg/m^2 in the absence of G ≥ 2 toxicity 3. Fixed dose (250, 350, or 500 mg/m^2) according to clinical and laboratory parameters.	164 patients, 3 groups: 1. Group A: n = 36: irinotecan 350 mg/m^2 2. Group B: n = 62: 250, 350, or 500 mg/m^2, according to individual patient tolerance 3. Group C: n = 66: Based on risk factor optimization Results: • Trend toward higher ORR in Group B (13%) than in Groups A (8%) and C (9%). • High tumor control growth rate in 3 groups: A, 58% group, B, 60% and C, 50% • Percent receiving 500 mg/m^2: B, 34% C, 9% • TTP: Groups A and B > Group C. • Dose escalation arm: 31% of patients reached highest dose level, had the best benefit/risk ratio. No significant differences for AEs. Conclusion: "Individual dose escalation based on patient tolerance may allow more patients to receive a higher irinotecan dose without causing additional toxicity and can be an appropriate patient management strategy."	Van Cutsem et al, 2005 [25]

mCRC = metastatic colorectal cancer; G = toxicity grade; GI = gastrointestinal; ORR = objective response rate; DCR = disease control rate; TTP = time to progression; PFS = progression-free survival; OS = overall survival; PD = progressive disease; 5-FU = 5-fluorouracil.

per cycle up to 293 mg/m²; 6/7 patients received 180 mg/m² then increased 20% per cycle up to 274 mg/m²; and 7/7 patients received 126 mg/m² then increased 10% per cycle according to tolerance up to 153 mg/m².

– Initial 5-FU for 46 hours after treatment with 200 mg/m² of IV leucovorin bolus and 400 mg/m² of IV bolus of 5-FU for 10 minutes [29]. The baseline initial 5-FU dose of 2,400 mg/m² was initially adjusted according to a multiparametric approach 5-FU$^{ODPM\ Tox}$ [15,35] and then tailored using PK monitoring 5-FU$^{ODPM\ Protocol}$ [15,35]. Treatment was continued until progression, or if severe toxicity took place, or according to the patient's or physician's decision.

Cetuximab was administered for 1.5 hours, 400 mg/m² on day 1 then 250 mg/m² weekly.

The sponsors of the study were informed of the results but did not contribute to any phase of the study design, collection, analysis and interpretation of the data, or the writing of the manuscript.

2.3. Methods

2.3.1. Genotyping

UGT1A1 gene was genotyped for UGT1A1*28 and UGT1A1*6 as previously described [29]. The analysis of *DPYD* polymorphisms and *UGT1A1* were based on pyrosequencing technology. Four single-nucleotide polymorphisms (SNPs) associated with severe DPD deficiency were systematically investigated (Table 6) [30].

2.3.2. 5-FU catabolism index

As previously described, the catabolism index was determined by using high-performance liquid chromatography (HPLC) to quantify endogenous uracil (U) and dihydrouracil (UH_2) and in turn determining the UH_2/U ratio [35].

2.3.3. Multiparametric approach

As previously described, the risk of toxicity to 5-FU was determined using the calculator 5-FU$^{ODPM\ Tox}$ [15] and when a risk of toxicity was detected, the clinician was provided a suggested initial dosage.

Table 5
Assessment of high-dose irinotecan in combination with 5-fluorouracil.

Regimen: Irinotecan combined with LV5FU2	Clinical dose-finding and PK study in 55 patients with pretreated mCRC. Irinotecan administered every 2 weeks at range of dose levels up to 260, 300 mg/m^2.	Doses of 180 or 200 mg/m^2 recommended but MTD not reached at 300 mg/m^2 Recommendation: FOLFIRI with irinotecan dose escalation up to 260 mg/m^2 (HD-FOLFIRI), with filgrastim (GCSF)	Ducreux et al, 1999 [26]
Irinotecan in mCRC: dose intensification and combination with new agents.		Conclusion: "It seems possible to safely escalate the dose of irinotecan to 500 mg/m^2 in patients showing good tolerance. In combination with LV5FU2, administer doses up to 260 mg/m^2."	Ducreux et al, 2003 [20]
Increasing doses of irinotecan combined with a simplified LV5FU2 regimen in metastatic colorectal cancer	Patients received FOLFIRI every 2 weeks for up to 6 cycles, comprising a 5-FU/LV regimen combined with irinotecan at 180 mg/m^2 (cycle 1), increasing to 220 mg/m^2 (cycle 2) and 260 mg/m^2 (cycle 3 and subsequent cycles) dependent on toxicity. Efficacy and safety determined in ITT population and in patients able to receive irinotecan at 260 mg/m^2 for at least four cycles [high-dose (HD) population]	54 patients: • Maximum dose 260 mg/m^2 (HD) in 44 patients (81.5%). • ORR: 48% (90%CI: 36–60) with 25/26 of the responses in HD arm. • DCR: 76% (90%CI: 65–85) • Median OS: 20.4 months. Toxicity HD/SD: • %G3/4 Neutropenia: 61 *v* 59 • %G3/4 Diarrhea: 18 *v* 11 Conclusion: HD irinotecan efficacy not better than conventional dose. Reduction of tumor volume by $\geq$ 75% in 50% of patients, no secondary resection of metastases. "Dose escalation must be reserved for patients with potentially resectable liver metastases"	Duffour et al, 2007 [27]
High-dose irinotecan plus LV5FU2 or for patients with metastatic colorectal cancer: a new way to allow resection of liver metastases?	High-dose irinotecan plus LV5FU2 or simplified LV5FU (HD-FOLFIRI) 60 patients with unresectable and measurable mCRC, Irinotecan 260 mg/m^2 with LV5FU2 in 25 patients, then HD-FOLFIRI in 35 patients.	HD-FOLFIRI: • ORR: 57% • DCR: 85%. • Secondary resection metastases: 28% HD-FOLFIRI vs LV5FU: • Median PFS: 10.1 *v* 7.8 months. • Acceptable toxicity but 45% of patients received G-CSF: • %Febrile neutropenia 11 *v* 12 • %G3/4 diarrhea 14 *v* 20 Conclusion: "HD-FOLFIRI is feasible, achieved high ORR and post-surgery CRR".	Ducreux et al, 2008 [28]

5-FU = 5-fluorouracil; HD = high dose; SD = standard dose; mCRC = metastatic colorectal cancer; G = toxicity grade; ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; OS = overall survival; 5-FU = 5-fluorouracil; FOLFOX = 5-FU + leucovorin + oxaliplatin; FOLFIRI = 5-FU + leucovorin + irinotecan.

2.3.4. Follow-up—Efficacy and tolerance assessment

Treatment efficacy was evaluated by comparing pretherapeutic metastatic lesions to those remaining after 3 months of treatment, confirmed 1 month later and every 3 months thereafter. Data were collected until the death of the patient or until the study termination date. Any treatment administered after progression under the FOLFIRI-cetuximab regimen was recorded. Tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) was assessed by the local investigators every 12 weeks using computed tomographic scans, and confirmed 1 month later [37]. Partial or complete response at 3 months was confirmed 1 month later. Disease control was defined as a complete or partial response, plus stable disease.

Table 6
DPYD gene mutations.

Exon	Nucleotide	Protein	Reference	NCBI SNP reference
22	A2846T	D949V	DPYD*9B	rs67376798
Intron 14	IVS14+1G > A	Exon 14 skipping	DPYD*2A	rs3918290
13	T1679G	I560S	DPYD*13	rs55886062
4	del TCAT 295-298	Frameshift	DPYD*7	rs72549309

Every 2 weeks, patients were examined and adverse toxic events were evaluated and graded. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 4.0. Doses of each agent were reduced following adverse events as specified in the study protocol. A cetuximab-related adverse cutaneous effect was defined as any adverse cutaneous effect other than hand–foot syndrome. Central chart review was performed for all patients who died within 30 days after the last administration of the study drugs and whose death was accompanied by any event other than disease progression, regardless of the reported cause. The results of the central review were submitted to the independent data and safety monitoring committee for final assessment. In the event of grade 2 toxicity due to irinotecan, the dose was reduced by 10%. For grade 3 toxicity due to irinotecan, the treatment was interrupted until the toxicity was grade $\leq$1 and treatment was restarted with a 25% decrease of irinotecan. Treatment was stopped in all cases of grade 4 toxicity. Treatment was continued until disease progression, death, or unacceptable adverse event, whichever came first.

2.4. Data analysis

OS was defined as the period between the start date of treatment and the date of death, regardless of cause. PFS was defined as

Table 7
Patients' initial characteristics.

Clinical data		No. (%)
Gender	Male	51 (60.0)
	Female	34 (40.0)
PS	0–1	73 (91.2)
	2	7 (8.8)
Median age		61.0 years
Range		38–79 years
Tumor site	Colon	48 (56.5)
	Rectum	26 (30.6)
Histology	Lieberkuhnian	75 (88.2)
Metastatic site		
No. of sites > 1		33 (38.8)
Site of metastase(s)	Liver	65 (76.5)
	Lung	36 (42.3)
	Peritoneal Metastases	7 (8.2)
	Nodes	12 (14.1)
Previous treatment (in first-line)		
LV5FU2		14 (15.3)
FOLFOX4		50 (58.8)
FOLFIRI without cetuximab		22 (25.9)
+ targeted therapy (bevacizumab)		20 (23.5)
Genotype		
DPYD 2846 A > T		1 (0,96)
DPYD IVS+1G > A		2 (1,92)
UGT1A1* 28 (6/6)		44 (51.7)
UGT1A1* 28 (6/7)		34 (40.0)
UGT1A1* 28 (7/7)		7 (8.2)

the period between the start date of treatment and the date of progression (clinical or radiological) or death. All results of efficacy were considered in patients in intention-to-treat. Patients without progression at the time of analysis were censored at their last available follow-up assessment. Well-known prognostic factors of survival, response, and toxicity were compared with each genotype by chi-square test or Fisher test, including number of metastatic sites (one ν more), PS at enrollment (Eastern Cooperative Oncology Group [ECOG] 0 or 1 ν 2), age (< 60, 61–70, and > 70 years), and gender. Prognosis factors of efficacy and safety were analyzed by logistic regression. The α-error risk was classically chosen at 5%. Statistical analysis was performed on SAS 9.1.3 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

A total of 85 patients were enrolled between December 2005 and February 2008. The median follow-up was 126 days (range, 1–582 days). Clinical characteristics of the population of patients are summarized in Table 7. Median age was 61 years (range, 38–79 years). ECOG PS was < 2 in 91.2% of patients. At the time of enrollment, 61.2% of patient had a single metastasis with liver metastases in 76.5% of these. Previously used chemotherapy regimens included LV5FU2 (15.3%), FOLFOX4 (58.8%), and FOLFIRI (25.9%). Bevacizumab had been administered to 20 patients (23.5%).

Table 8
Irinotecan dosing escalation along the treatment.

	Irinotecan			Cycle no.	Dose at 3 months
	n	Mean dose in mg/m²	[min; max]	mean	Mean dose in mg/m²
6/6	44	224 ± 37	[150; 299]	8 ± 6	247 ± 50
6/7	34	196 ± 36	[137; 274]	9 ± 7	210 ± 53
7/7	7	135 ± 14	[117; 153]	10 ± 5	140 ± 21

3.2. 5-FU and irinotecan dose adjustment

The distribution of *UGT1A1* and *DPYD* polymorphsms is in agreement with the literature (Tables 7 and 8). *UGT1A1* genotypes found were variant *28/*28, ie, 7/7 in 8.2% of patients, 6/7 in 40%, and 6/6 in 51.7%. In accordance with protocol guidelines, the 34 (40%) patients with 6/7 variants had an initial irinotecan dose of 180 mg/m². Five patients (4.8%) presented with major but not total DPD deficiency. Three of the five had relevant heterozygous *DPYD* polymorphisms.

The chi-square statistic test when suitable, or Fisher test when one of the theoretical numbers was < 5, did not show significant differences in terms of gender, age, or PS in the polymorphisms-based subpopulations.

Sixty-four patients (75.3%) received at least six cycles of treatment, 27 (31.7%) received 12 cycles, and nine patients (10.5%) received 18 cycles. A total of five patients (5.8%) initially received a reduced dose of 5-FU; these included the four patients in whom DPD deficiency had been detected pretherapeutically and an 80-year-old patient. Following the recommendations provided by the 5-FU$^{ODPM\ Tox}$ algorithms, these five patients received 5-FU dosages that were reduced 30%–70% (720–1,700 mg/m²) compared to the standard dose (2,400 mg/m^2), with dosages then adjusted at every cycle based on PK values [15,29]. All other patients received standard initial doses of 5-FU (2,400 mg/m^2). Mean 5-FU dose at 3 months for the whole population was 2,412 ± 364 mg/m^2 with a wide dosing variability to reach the targeted AUC (1,615–3,170 mg/m^2). Throughout all cycles of the entire treatment, dosages varied widely between individuals: from 1,900–7,000 mg (722–4,117 mg/m²), the latter being nearly twice the initial dose, without specific adverse events.

All seven of the patients homozygous for UGT1A1*28 (7/7) received at least six cycles of treatment and three of the seven (42.8%) at least 12 cycles, at a mean irinotecan dose of 135 ± 14 mg/m² (range, 117–153 mg/m²). The irinotecan mean dose administered to patients with the 6/6 genotype was 224 ± 37 mg/m² (range, 150–299 mg/m²), while patients with the 6/7 genotype received 196 ± 36 mg/m² (range, 137–274 mg/m²) (Table 8).

3.3. Toxicity study/analysis

3.3.1. Toxicity in the overall population

The majority (76.7%) of adverse events were grades 1–2, and were mainly gastrointestinal (28.9%) and skin (18.7%) toxicities, related to the use of cetuximab. Fifteen percent of toxicities were grade 3–4 and 27% of these were gastrointestinal (16.5% grade 3 diarrhea), However, no grade 4 diarrhea was reported in those with 6/6 or 6/7 genotypes despite the increased doses of irinotecan (Table 9). Hematologic toxicities were recorded in 30.5% of patients including grade 4 toxicities in 5.9%, primarily neutropenia; while 45.8% of patients had either no or only grade 1 hematologic toxicity. Neutropenia was expected since the irinotecan dosage in patients with the 6/6 and 6/7 genotypes was incrementally increased until a significant adverse event occurred.

Two deaths were reported, both due to pulmonary embolism, not attributable to the treatment according to the investigator.

Considering the highest grade of toxicity per patient, no significant differences in terms of neutropenia and diarrhea were found when comparing outcomes in the *UGT1A1* polymorphism subgroups. Furthermore, it is noteworthy that neither grade 4 neutropenia nor grade 4 diarrhea were reported in the patients with *28/*28 (or 7/7) genotype.

Table 9
Neutropenia and diarrhea observed per patient for the whole treatment according to the UGT1A1 genotype.

Toxicity	Genotype (n)		Grade I n (%)	Grade II n (%)	Grade III n (%)	Grade IV n. (%)
Neutropenia	6/6	(44)	0	14 (31.8)	11 (25.0)	3 (6.8)
	6/7	(34)	0	16 (47.0)	10 (29.4)	2 (5.8)
	7/7	(7)	1 (14.3)	4 (57.1)	1 (14.3)	0
Diarrhea	6/6	(44)	20 (45.5)	13 (29.5)	8 (18.2)	0
	6/7	(34)	16 (47.0)	7 (20.6)	5 (14.7)	0
	7/7	(7)	4 (57.1)	6 (85.7)	1 (14.3)	0

3.4. Response study/analysis

3.4.1. Objective response

The objective response rate observed was 25.8% in the whole population of patients (Table 10). Thirty-seven patients (43.5%) were able to undergo a secondary resection of metastases. Twenty-seven of the 37 patients (31.7% of all patients) had secondary resection of liver metastases, while the others had secondary resections of lung and ovarian metastases. No variable had a significant effect on the ORR. A trend could not be clearly identified because the confidence interval (CI) of each variable contained the value 1. Furthermore, the *P* values were far removed from .05 and even .25, the threshold value often used in a multivariate analysis.

3.4.2. Response according to UGT1A1 status

The rates of disease control were remarkably similar among the three groups with different *UGT1A1* genotypes: 55.9% to nearly 59.1% (Table 10). The response rate in patients with the *28/*28 (7/7) genotype was the same as the two other groups of patients who were given considerably higher dosages ($P = .7394$).

3.4.3. Response according to KRAS status—Retrospective analysis

Response rates and PFS according to *KRAS* status were performed retrospectively. ORRs in patients with tumors harboring wild-type (WT)-*KRAS* and mutant (MT)-*KRAS* were 58% and 25%, respectively. In MT-*KRAS*, the ORR was 57.3% in second line with a 3-month disease-control rate of 80%.

3.5. PFS analysis

The median PFS in the overall population was 181 days [94; 201]. Interestingly, the median PFS in the three UGT1A1 subgroups were not statistically different (200, 132, and 121 days for patients with the 6/6, 6/7, and 7/7 genotypes, respectively) ($P = .5002$) (Fig. 1).

In a Cox semi-parametric model on the standard population, no variables concerning the clinical, biological or pharmacogenetic data appeared significant, suggesting the UGT1A1*28/*28 (7/7) genotype is not predictive of a lower PFS.

Table 10
Response to treatment after 3 months according to UGT1A1 status.

Responses	UGT1A1 genotype, n (%)		
	6/6	6/7	7/7
No. of patients	44 (51.7)	34 (40.0)	7 (8.2)
Objective response (OR)	10 (22.7)	9 (26.5)	3 (42.8)
Stable disease (SD)	16 (36.4)	10 (29.4)	1 (14.3)
Controlled disease (OR and SD)	26 (59.1)	19 (55.9)	4 (57.1)
Progressive disease	10 (22.7)	9 (26.5)	2 (28.6)
Not evaluable	8 (18.2)	6 (17.6)	1 (14.3)

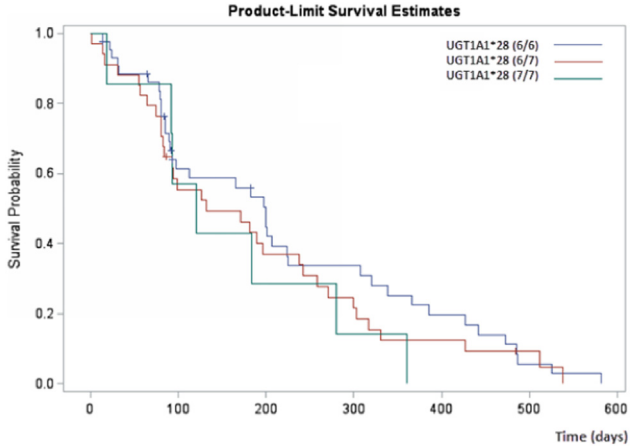

Fig. 1. Progression-free survival curves of patients based on UGT1A1 *28 genotypes. The curves are identical with individually adapted dose.

4. Discussion

To our knowledge, this is the first phase II study to report the clinical efficacy and toxicity of a FOLFIRI-cetuximab regimen in 85 patients in which both irinotecan and 5-FU doses were tailored and individually adjusted based on *DPYD* and *UGT1A1* genotyping as well as 5-FU PK monitoring.

Pretherapeutic screening (5-FU$^{\text{ODPM Tox}}$) and 5-FU dose monitoring (5-FU$^{\text{ODPM Protocol}}$) likely contributed to the mild 5-FU toxicity. A 16.5% incidence of grade 3 diarrhea in the study population appears lower than data reported in the literature [38]. The low incidence of toxicity occurred despite very large increases in dose, up to 4,117 mg/m², and the very broad range of individual doses administered to achieve targeted plasma concentration.

Regarding irinotecan, our data show, like others, that patients with the *UGT1A1* 6/6 genotype are currently receiving suboptimal doses since we were able to increase the initial dose of 180 mg/m² an average of 40% at 3 months and 50% at 6 months [17–19]. Indeed, at an irinotecan dose of 180 mg/m², only patients with the 6/7 genotype, estimated at 40% of the population, are appropriately dosed whereas patients with the 6/6 or 7/7 genotypes are receiving insufficient or excessive doses of irinotecan, respectively. Because we sought to identify the maximum tolerated dose especially for patients with the 6/6 genotype but also those with the 6/7 genotype, a 33.3% incidence of grade 3/4 neutropenia was observed in this second-line population of patients, already exposed to cytotoxic drugs. This incidence of toxicity is similar to what was reported in the CRYSTAL study, in first-line treatment, with no dose intensification (28.2% and 15.7%, respectively) [39]. In contrast, because the dose administered to patients with the 7/7 genotype was reduced 30% and not increased, there were no grade 4 toxicities recorded in these patients.

An ORR of 25.8% in the general population was encouraging given patients were receiving their therapy as second line and only 40% received cetuximab because *KRAS* was not routinely genotyped at the time they enrolled. In a post hoc assessment, the ORR in those with WT-KRAS was 57.3%. Our response rate in second line is equivalent to the ORR in first line in the CRYSTAL study and comparable to that in the CELIM phase II trial where neo-adjuvant chemotherapy was given to patients with liver metastasis and the 35% ORR using panitumumab + FOLFIRI in patients with WT-*KRAS* tumors after progression on FOLFOX [10,40,41]. Furthermore, in 27 patients (31.7%) in this second-line setting, the favorable response allowed them to undergo a secondary R0/R1 resection of liver metastases. This percentage in an unselected population of

patients is remarkable because it is quite comparable to the percentages obtained with more toxic regimens in first-line setting in liver-limited metastatic cancer patients (Table 1). Noteworthy, despite a very wide range of irinotecan dosage, we did not observe differences, in efficacy nor tolerance in the three groups of patients. This is consistent with our hypothesis that the lower ORR and shorter PFS reported for patients homozygous for seven TATA repeats (7/7) is likely due to the higher rate of toxicity and treatment delays. Using the approach we describe here patients with the 7/7 UGT1A1 genotype had the same opportunity to respond to treatment as the other groups, and markedly improved tolerance.

In a small phase II study of 26 patients, efficacy and tolerance of induction chemotherapy combining conventional LV5FU2 with increased doses of irinotecan and cetuximab adapted to UGT1A1 genotyping have been assessed in untreated, potentially resectable liver metastases of colorectal cancer. Irinotecan was given at 260 mg/m^2 for UGT1A1 6/6 and 6/7 genotypes and 220 mg/m^2 for UGT1A1 7/7 genotypes with conventional BSA-based doses of 5-FU. Primary prevention with lenograstim (days 5–9) was given to UGT1A1 6/7 and 7/7 genotypes. Among 23 assessable patients, the objective response rate was 82.6 % and 21 patients (80.7 %) had a metastasis resection, but 31% grade 3–4 neutropenia and 20.8% diarrhea were reported.

Besides, in a parallel PK/PD study performed to provide an initial insight that will guide future studies evaluating cetuximab dose adjustments, we found a close correlation between the AUC of cetuximab and PFS, an observation that warrants further investigation [36].

In a review on high-dose irinotecan in combination with a simplified LV5FU2 (HD-FOLFIRI) regimen, the authors, like other investigators, acknowledged the frequent under-dosing that occurs with BSA-based irinotecan and recommended irinotecan dose escalation in carefully selected patients: young patients with good PS (WHO 0 or 1) and normal liver function, with metastases that could become resectable in the case of a major tumor response. In the absence of UGT1A1 assessment they proposed to administer the first course at a dose of 220 mg/m^2, then increase the dose to 260 mg/m^2 for the following cycles if it was well tolerated. Finally, they recommended preliminary UGT1A1 genotyping to get faster to the optimal dosing [42]. Based on UGT1A1 genotyping, we thus recommend (1) giving up to 250 mg/m² irinotecan in the first cycle to patients with the *UGT1A1* 6/6 genotype; (2) prudently increasing from 180 mg/m^2 by 20% at each cycle up to 250 mg/m² for those with the 6/7 genotype; and (3) starting patients with the 7/7 genotype at 130 mg/m². For 5-FU, it is essential pretherapeutic screening using a multiparametric approach (5-FU$^{\text{ODPM Tox}}$) be performed in order to detect patients at risk of severe early-onset toxicity. Subsequently, individual PK monitoring (5-FU$^{\text{ODPM Protocol}}$) enables the clinician to determine the correct dosage rapidly.

This individual dose adjustment of both 5-FU alone as well as irinotecan and 5-FU combined with cetuximab allowed us to safely, quickly and efficiently reach the intensified optimal dosages and favorably compares both in terms of efficacy and safety with other cytotoxic high-dose bitherapies combined with targeted therapies, such as vascular endothelial growth factor (VEGF) or epidermal growth factor (EGF) antibodies, often needing G-CSF coverage (Table 5). It favorably compares with tritherapies as well, such as FOLFIRINOX and FOLFOXIRI combined or not with targeted therapies, where its widespread use has been hampered by their high level of severe toxicity, limiting them to young patients, with a PS 0–1, and no liver impairment (Table 1).

In conclusion, to our knowledge, this is the first study that provides proof of concept for cytotoxic drug personalization in clinical practice. Genotyping *DPYD* and *UGT1A1* prior to the start of therapy, combined with 5-FU PK monitoring, can offer individual patients the optimal dosage with a fully manageable toxicity profile.

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