

Clinical Study

Effectiveness and Safety of Intensive Triplet Chemotherapy Plus Bevacizumab, FIr-B/FOx, in Young-Elderly Metastatic Colorectal Cancer Patients

Gemma Bruera,^{1,2} Katia Cannita,¹ Aldo Victor Giordano,³ Roberto Vicentini,⁴ Corrado Ficorella,^{1,2} and Enrico Ricevuto^{1,2}

¹ Medical Oncology, S. Salvatore Hospital, University of L'Aquila, 67100 L'Aquila, Italy

² Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, 67100 L'Aquila, Italy

³ Radiology, S. Salvatore Hospital, 67100 L'Aquila, Italy

⁴ Hepatobiliar-Pancreatic Surgery, S. Salvatore Hospital, 67100 L'Aquila, Italy

Correspondence should be addressed to Enrico Ricevuto; enrico.ricevuto@univaq.it

Received 26 June 2013; Revised 31 August 2013; Accepted 13 September 2013

Academic Editor: Hidekazu Kuramochi

Copyright © 2013 Gemma Bruera et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Four-drug regimens, such as FIr-B/FOx schedule, can improve efficacy of first-line treatment of metastatic colorectal cancer (MCRC) patients. The present study specifically evaluates feasibility of FIr-B/FOx first-line intensive regimen in fit young-elderly MCRC patients, representing approximately 40% of overall MCRC patients. Activity, efficacy, and safety were equivalent to overall MCRC patients, not significantly different according to *KRAS* genotype. Clinical outcome was significantly prolonged in liver-limited compared to other/multiple metastatic disease. Safety evaluation of the individual young-elderly patient showed that limiting toxicity syndromes (LTS) in multiple sites were significantly increased, compared to LTS in single site, with respect to non-elderly patients.

1. Introduction

Clinical management of MCRC is faced with different options and lines of treatment according to patients' fitness, extension of metastatic disease, and *KRAS* genotype [1–6]. First line triplet regimens of chemotherapeutic drugs, or doublet associated to bevacizumab (BEV) or cetuximab, reported in phase III trials objective response rate (ORR) 39%–68%, progression-free survival (PFS) 7.2–10.6 months, and overall survival (OS) 19.9–26.1 months [2, 4, 6–8]. More intensive triplet chemotherapy plus targeted agents can further achieve ORR 82%, liver metastasectomies 26%, PFS 12 months, OS 28 months [1–5]. In liver-limited (L-L) disease, metastasectomies were 54%, and clinical outcome was significantly improved, particularly in *KRAS* wild-type patients [3, 5].

Older patients are usually underrepresented in clinical trials, despite the increased incidence with age, and often undertreated in clinical practice. Retrospective studies showed similar safety and efficacy in fit elderly compared to

younger patients [9–11]. Elderly patients require a decision-making process including functional, nutritional, and comorbidity status to discriminate fitness and tailor medical treatment [12]. Fit patients ≥ 70 years benefit from 5-fluorouracil (5-FU) as younger patients: ORR 23.9%, PFS 5.5 months, and OS 10.8 months [13]. A retrospective review and a pooled analysis reported no different activity and efficacy [14, 15]. The same benefit was reported from irinotecan (CPT-11) containing chemotherapy in fit older ≥ 70 years [16]; age was not an independent prognostic factor for OS [17]. The significantly improved relative benefit of FOLFOX did not differ by age [18]. In the OPTIMOX1 trial, ORR 59%, median PFS 9.0 months, and median OS 20.7 months were comparable in old-elderly patients [19]. In the FOCUS2 trial, specifically designed to evaluate first line reduced-dose (80%) of 5-FU or capecitabine with or without oxaliplatin (OXP), in old-elderly and/or frail patients, addition of OXP significantly improved ORR, and trendly PFS, but not OS [20]. Treatment efficacy was consistent across subgroups,

including age, when BEV was combined with CPT-11-based therapy [21]. In fit elderly patients, addition of BEV to 5-FU based chemotherapy significantly prolonged PFS (9.2–9.3 months) and OS (17.4–19.3 months) [22, 23]. In BRiTE and BEAT studies, no different PFS was observed; median OS decreased with age [24, 25]. No impact on PFS and OS was observed by age and/or comorbidities in patients treated with FOLFOX or FOLFIRI added or not to cetuximab [26]. Addition of panitumumab to FOLFOX showed no clear benefit in PFS in elderly and performance status 2 patients [27].

In the randomized phase III trial comparing FOLFOXIRI with FOLFIRI, age was not a significant factor for activity and efficacy; elderly patients showed median OS 16.9 and 19.9 months with FOLFIRI or FOLFOXIRI, respectively [28, 29]. ORR was significantly lower in older patients treated with FOLFOXIRI [29]; no differences were reported in PFS and OS. Patients underwent metastasectomies without increased morbidity or mortality, irrespective of age.

Here, we report a retrospective analysis evaluating activity, efficacy, and safety of first-line FIr-B/FOx intensive regimen and the prognostic value of extension of metastatic disease [4, 5] in fit young-elderly MCRC patients enrolled in a previously reported phase II study [1] and in the expanded clinical program proposing first-line FIr-B/FOx treatment.

2. Materials and Methods

2.1. Patient Eligibility. Present retrospective analysis evaluated consecutive young-elderly patients 65 to 75 years enrolled in a previously reported phase II study [1] and in the expanded clinical program proposing first-line FIr-B/FOx treatment. Patients who were eligible were with histologically confirmed diagnosis of measurable MCRC, performance status ≤ 2 , adequate hematological, renal, and hepatic functions, and life expectancy > 3 months. Patients were not eligible if they showed uncontrolled severe diseases; cardiovascular disease (uncontrolled hypertension, uncontrolled arrhythmia, and ischemic cardiac diseases in the last year); thromboembolic disease, coagulopathy, and preexisting bleeding diatheses; proteinuria > 1 g/24 h urine; surgery within the previous 28 days before. Cumulative Index Rating Scale (CIRS) was used to evaluate the comorbidity status, and only patients with primary and intermediate CIRS stage were enrolled [12]. Primary CIRS stage consisted of independent Instrumental Activity of Daily Living (IADL) and absent or mild grade comorbidities; intermediate CIRS stage consisted of dependent or independent IADL and less than 3 mild or moderate grade comorbidities. Patients with secondary CIRS stage, consisting of more than 3 comorbidities or a severe comorbidity, with or without dependent IADL, were not enrolled. The study was approved by the Local Ethical Committee (Comitato Etico, Azienda Sanitaria Locale n.4 LAquila, Regione Abruzzo, Italia) and conducted in accordance with the Declaration of Helsinki. All patients provided written, informed consent.

3. Methods

3.1. Schedule. FIr-B/FOx regimen consisted of weekly timed flat-infusion/5-fluorouracil (TFI 5-FU) [30, 31], associated to weekly alternating CPT-11/BEV or OXP [1]: TFI 5-FU (Fluorouracil Teva; Teva Italia, Milan, Italy), 900 mg/m²/day, over 12 h (from 10:00 pm to 10:00 am), days 1, 2, 8, 9, 15, 16, 22, and 23; CPT-11 (Campto; Pfizer, Latina, Italy), 160 mg/m², days 1, 15; BEV (Avastin; Roche, Welwyn Garden City, UK), 5 mg/kg, days 1, 15; l-OXP (Eloxatin; Sanofi-Aventis, Milan, Italy), 80 mg/m², days 8, 22; cycles every 4 weeks.

3.2. Mutational Analysis. Genetic analyses were performed on paraffin-embedded tissue blocks from the primary tumor and/or metastases, as previously reported [5]. Genotype status was assessed for *KRAS* codon 12, 13, and *BRAF* c.1799 T>A (V600E) mutations by SNaPshot multiplex assay in 17 samples, as elsewhere reported [32, 33]. Briefly, *KRAS* exon 2 and *BRAF* exon 15 were simultaneously PCR-amplified and analyzed for *KRAS* c.34G, c.35G, c.37G, c.38G, and *BRAF* c.1799T mutations using the ABI PRISM SNaPshot Multiplex kit (Applied Biosystems, Foster City, CA, USA). *KRAS* exon 2 direct sequencing was performed using the Big Dye V3.1 Terminator Kit (Applied Biosystems, Foster City, CA, USA). Labelled products were separated in ABI Prism 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and analysed using the GeneMapper Analysis Software version 4.0 (Applied Biosystems, Foster City, CA, USA).

3.3. Study Design. Response was evaluated by computed tomography scan; positron emission tomography was added based on investigators' assessment. Follow-up was scheduled every three months up to progression or death. Resectability, defined according to reported categories [3], was evaluated in patients with L-L metastases every three cycles by a multidisciplinary team, consisting of a medical oncologist, liver surgeon, and radiologist, and recommended > 4 weeks after BEV discontinuation. Liver metastasectomies were defined as R0, if radical surgery, R1, if radioablation was added.

Toxicity was registered according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Limiting toxicity (LT) was defined as grade 3–4 non-hematological toxicity, grade 4 hematologic toxicity, febrile neutropenia, or any toxicity determining > 2 weeks treatment delay. To discriminate individual safety, limiting toxicity syndromes (LTS), consisting of at least an LT associated or not to other limiting or G2 toxicities, were evaluated, as previously reported [1]. LTS were classified as limiting toxicity syndromes single site (LTS-ss), characterized only by the LT, and limiting toxicity syndromes multiple sites (LTS-ms), ≥ 2 LTs or an LT associated to other, at least G2, non-limiting toxicities. Chi-square test was used to compare the rates of LTS-ms and LTS-ss [34].

Clinical criteria of activity and efficacy were ORR, PFS and OS. ORR was evaluated according to RECIST criteria [35]; pathologic complete response was defined as absence of residual cancer cells in surgically resected specimens. PFS

TABLE 1: Young-elderly patients' features.

	Overall Total no. (%)	KRAS wild-type Total no. (%)	KRAS mutant Total no. (%)
No. of patients	28	13 (50)	13 (50)
Sex			
Male/female	14/14	6/7	8/5
Age, years			
Median	67	67	68
Range	65–73	65–73	66–73
WHO performance status			
0	25 (89)	12 (92)	11 (85)
1-2	3 (11)	1 (8)	2 (15)
CIRS stage			
Primary	2 (7)	—	2 (15)
Intermediate	26 (93)	13 (100)	11 (85)
Metastatic disease			
Metachronous	10 (36)	5 (38)	5 (38)
Synchronous	18 (64)	8 (62)	8 (62)
Primary tumor			
Colon	15 (54)	5 (38)	10 (77)
Rectum	13 (46)	8 (62)	3 (23)
Sites of metastases			
Liver	17 (61)	7 (54)	8 (62)
Lung	9 (32)	4 (31)	4 (31)
Lymph nodes	10 (36)	4 (31)	5 (38)
Local	7 (25)	4 (31)	3 (23)
Other	5 (18)	1 (8)	4 (31)
No. of involved sites			
1	14 (50)	8 (62)	5 (38)
≥2	14 (50)	5 (38)	8 (62)
Single metastatic sites			
Liver-limited	8 (29)	4 (31)	3 (23)
Other than liver	7 (25)	4 (31)	2 (15)
Lung	4 (14)	2 (15)	1 (8)
Lymph nodes	1 (4)	1 (8)	—
Local	2 (7)	1 (8)	1 (8)
Multiple metastatic sites	13 (46)	5 (38)	8 (62)
Liver metastases			
Single	8 (29)	5 (38)	3 (23)
Multiple	9 (32)	2 (15)	7 (54)
Previous adjuvant chemotherapy	6 (21)	3 (23)	2 (15)
FA/5-FU bolus	3 (11)	2 (15)	—
FOLFOX4	3 (11)	1 (8)	2 (15)
Previous radiotherapy	2 (7)	2 (8)	—
RT + CT (5-FU continuous infusion)	2 (7)	2 (8)	—
RT + CT (XELOX)	—	—	—

WHO: world health organization; CIRS: cumulative illness rating scale.

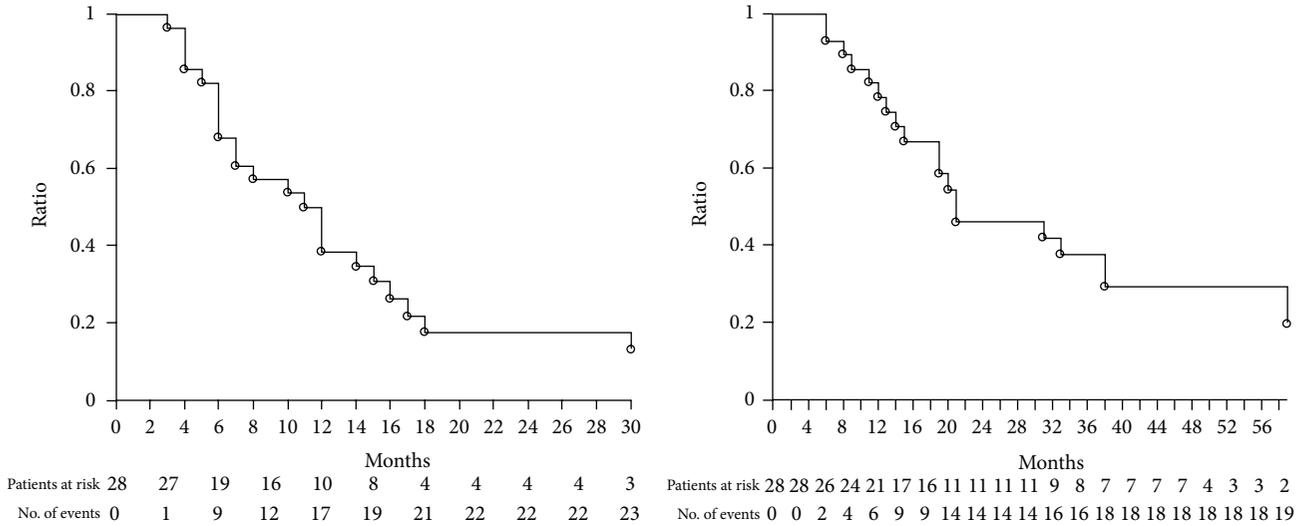
and OS were evaluated using the Kaplan-Meier method [36]. PFS was defined as the length of time from the beginning of

treatment and disease progression or death (resulting from any cause) or to the last contact and OS as the length of time between the beginning of treatment and death or to last contact. Log-rank test was used to compare PFS and OS according to *KRAS* genotype and metastatic extension, L-L versus other or multiple metastatic (O/MM) [37].

4. Results

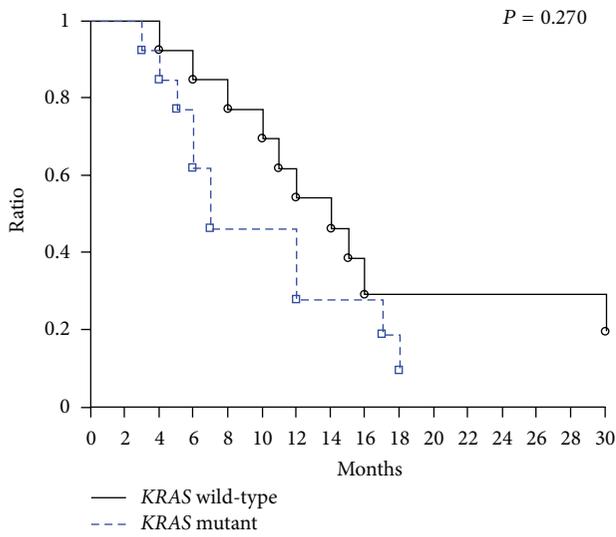
4.1. Patient Demographics. From March 2006 to November 2011, 28 young-elderly patients were enrolled among overall MCRC patients (42%); 26 (93%) were evaluable for *KRAS* genotype, 13 wild-type, and 13 mutant (Table 1). Patients fitting for intensive FIr-B/FOx treatment, according to inclusion criteria, represented 44% of consecutively observed MCRC patients, and this rate was equivalent for fit young-elderly patients. Demographic and baseline features were representative of the overall phase II study population: WHO Performance Status 0, 25 (89%), CIRS primary/intermediate, 2/26. Liver metastases affected 17 patients (61%), L-L 8 patients (29%), and O/MM 20 patients (79%). *KRAS* mutations were not differently represented with respect to overall MCRC patients (see, Supplementary material Table 1 at <http://dx.doi.org/10.1155/2013/143273>, which describes *KRAS* mutations): c.35 G>A (G12D), 8 (30.7%); c.35 G>T (G12V), 3 (11.5%); c.35 G>C (G12A), 1; c.38 G>A (G13D), 1. Seventeen tumoral samples (65%) were also analyzed for *BRAF*, and no mutation was detected.

4.2. Activity and Efficacy. In the intent-to-treat analysis of 28 evaluable young-elderly patients, ORR was 79% (α 0.05, CI \pm 15) (Table 2). We observed 22 objective responses: 19 partial (68%) and 3 clinical complete (CR 11%), 1 stable (4%), and 5 progressive diseases (18%). Disease control rate was 82% (α 0.05, CI \pm 14). After a median follow-up of 17 months, median PFS was 11 months (3–78+). Median OS was 21 months (6–78+) (Figures 1(a) and 1(b)). Liver metastasectomies were performed in 5 pts (18%): 3 out of 8 L-L pts (37.5%). In one *KRAS* wild-type patient with single liver associated with lung metastases, double metastatic resections were performed. In one *KRAS* mutant patient with single liver associated with single lung metastasis, liver metastatic resection was performed, and a clinical CR of lung metastasis was obtained. Overall, R0 liver resections were 4 (80%) and R1 resection was 1 (20%). No surgery-related complications were reported. Overall, 3 clinical plus 2 pathologic CRs were reported (18%): 2 clinical CR in *KRAS* wild-type patients and 3 in *KRAS* mutant patients (1 clinical CR and 2 pathologic CR). Pathologic CRs were obtained in 2 *KRAS* mutant patients, harboring c.35 G>T and c.35 G>A mutations, with multiple L-L metastases and single liver plus single lung metastases, respectively, who obtained a clinical partial response after treatment. One patient progressed at 17 months; 4 patients were progression-free at 78, 69, 49, and 10 months. Overall, 16 patients (57%) received a second line treatment: FIr-B/FOx rechallenge, 3 (19%); cetuximab-containing treatment, 9 (56%); BEV-containing, 1 (6%); panitumumab, 1 (6%);

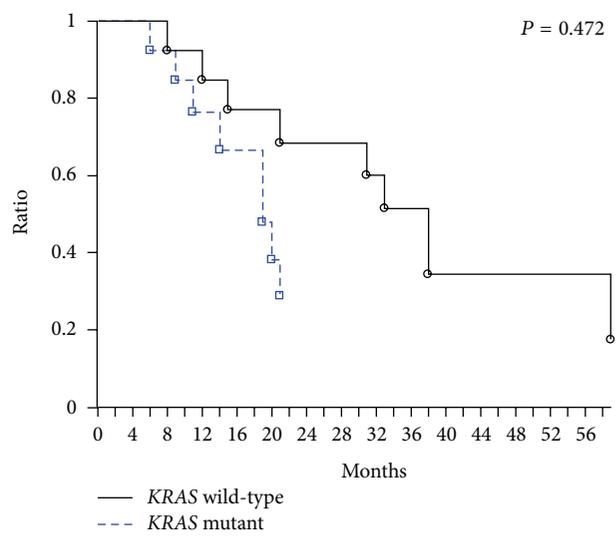


(a) 11 months (3-78+)

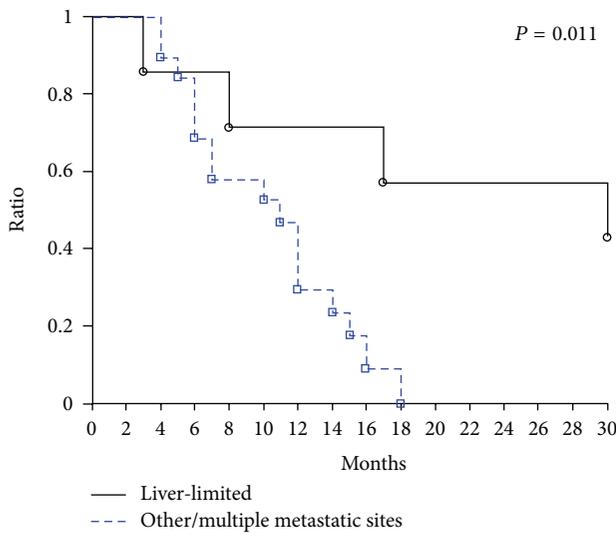
(b) 21 months (6-78+)



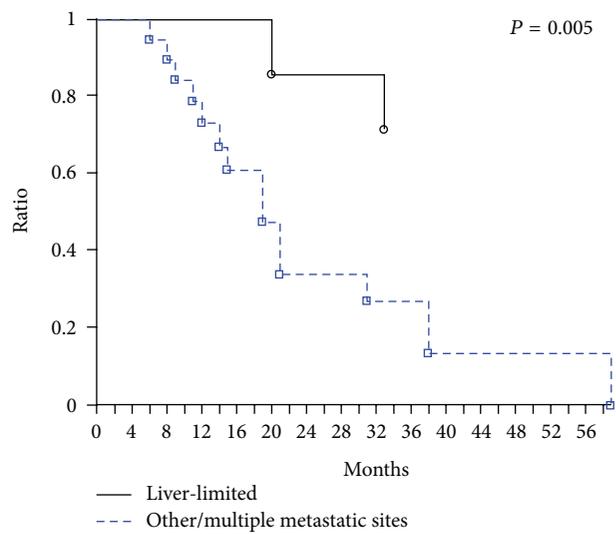
(c)



(d)



(e)



(f)

FIGURE 1: Legend Kaplan-Meier survival estimate: (a) overall population, progression-free survival; (b) overall population, overall survival; (c) overall population *KRAS* wild-type versus *KRAS* mutant, progression-free survival; (d) overall population *KRAS* wild-type versus *KRAS* mutant, overall survival; (e) liver-limited versus other/multiple metastatic sites, progression-free survival; (f) liver-limited versus other/multiple metastatic sites, overall survival.

TABLE 2: Activity, efficacy, and effectiveness of FIr-B/FOx regimen in young-elderly patients according to *KRAS* genotype.

	All		<i>KRAS</i> wild-type		<i>KRAS</i> mutant	
	Intent-to-treat analysis		Intent-to-treat analysis		Intent-to-treat analysis	
	No.	%	No.	%	No.	%
Enrolled pts	28	100	13	100	13	100
Evaluable pts	28	100	13	100	13	100
Objective response	22	79 (CI ± 15)	12	92 (CI ± 15)	10	77 (CI ± 24)
Partial response	19	68	10	77	9	69
Complete response	3	11	2	15	1	8
Stable disease	1	4	—	—	1	8
Progressive disease	5	18	1	8	2	15
Median PFS, months	11		14		7	
Range	3–78+		4–78+		3–69+	
Progression events	23	82	10	77	11	85
Median OS, months	21		38		19	
Range	6–78+		8–78+		6–69+	
Deaths	19	68	9	69	8	61.5
Liver metastasectomies	5		3		2	
No/overall pts	5/28	18	3/13	23	2/13	15
No/Pts with liver metastases	5/17	29	3/7	43	2/8	25
No/Pts with L-L metastases	3/8	37.5	2/4	50	1/3	33
Pathologic complete responses	2	40	—	—	2	100

pts: patients; PFS: progression-free survival; OS: overall survival; L-L: liver-limited.

capecitabine, 1 (6%); surgery, 1 (6%). Most *KRAS* wild-type patients received a second line anti-EGFR-containing treatment (7 out of 9, 78%); BEV-containing, 1 (11%); surgery, 1 (11%). Seven patients (25%) received a third line treatment: cetuximab-containing treatment, 2 (28.5%); panitumumab, 3 (43%); capecitabine, 2 (28.5%). Three patients (11%) received a fourth line treatment: CPT-11, 1 (33%); raltitrexed, 1 (33%); capecitabine, 1 (33%). Three patients (11%) received treatment beyond the fourth line: fifth line cetuximab-containing treatment, 1 (33%), raltitrexed, 1 (33%); sixth line capecitabine, 1 (33%).

Among 13 *KRAS* wild-type patients, ORR was 92% (α 0.05, CI ± 15) (Table 2). We observed 12 objective responses: 10 partial (77%) and 2 CR (15%) and 1 progressive disease (8%). Liver metastasectomies were performed in 3 patients (23%), 2 out of 4 L-L (50%). Median PFS was 14 months (4–78+ months). Median OS was 38 months (8–78+ months). Among the 9 *KRAS/BRAF* wild-type patients, ORR was 89% (α 0.05, CI ± 22), median PFS was 11 months (4–49+ months), and median OS was 23 months (8–59 months). Among 13 *KRAS* mutant patients, ORR was 77% (α 0.05, CI ± 24). We observed 10 objective responses: 9 partial (69%) and 1 CR (8%), 1 stable (8%), and 2 progressive diseases (15%). Disease control rate was 85% (α 0.05, CI ± 20). Liver metastasectomies were performed in 2 patients (15%) out of 8 L-L (20%). Median PFS was 7 months (3–69+ months). Median OS was 19 months (6–69+ months). *KRAS* wild-type compared with mutant patients did not show significantly different PFS nor OS (Figures 1(c) and 1(d)).

4.3. *Dose-Intensity and Toxicity.* Median number of cycles per patient was 5 (range 2–9). Median received dose intensities (rDI) per cycle were equivalent to overall patients: 5-FU 1440 (480–1800) mg/m²/w, 80%; CPT-11 64 (25–80) mg/m²/w, 80%; I-OMP 32 (8–40) mg/m²/w, 80%; BEV 2 (1–2.5) mg/kg/w, 80% (see Supplementary material, Table 2, which describes rDI).

One patient (3.5%) discontinued FIr-B/FOx treatment due to limiting toxicity (grade 3 diarrhea). G3-4 toxicities, by patients, in 134 cycles, were (Table 3) diarrhea, 6 (21%); stomatitis/mucositis, 3 (11%); asthenia, 3 (11%); and neutropenia 3 (11%). The prevalent toxicity was diarrhea, G2-G3 in 14 patients (50%), similar to non-elderly [1]. G2 toxicities were nausea 11 (39%), vomiting 3 (11%), diarrhea 8 (29%), asthenia 11 (39%), neurotoxicity 4 (14%), hypertension 3 (11%), and neutropenia 11 (39%). No cases of thrombosis, hemorrhage/bleeding, cardiac or cerebrovascular ischemia, G4 neutropenia, febrile neutropenia, severe thrombocytopenia, or toxic deaths were observed. LTS were observed in 13 out of 28 young-elderly patients (46%) (Table 4): LTS-ms, 11 pts (39%) and LTS-ss, 2 pts (7%). LTS-ms were characterized by: LT associated to other, at least G2, non-limiting toxicities, 9 pts (32%); and ≥2 LTs, 2 pts (7%). LTS were significantly represented by LTS-ms compared to LTS-ss (chi-square 3.832, P = 0.05), with respect to non-elderly patients. LTS were (see Supplementary material, Table 3, which describes toxicities characterizing LTS in individual patients) G2-3 diarrhea-associated, 9 patients (69.2%), 8 LTS-ms and 1 LTS-ss; G3 mucositis associated with G3 erythema,

TABLE 3: Cumulative toxicity.

Number	Patients				Cycles			
	28				134			
NCI-CTC Grade	1	2	3	4	1	2	3	4
Nausea (%)	10 (36)	11 (39)	2 (7)	—	43 (32)	18 (13)	2 (1.5)	—
Vomiting (%)	7 (25)	3 (11)	2 (7)	—	15 (11)	5 (4)	2 (1.5)	—
Diarrhea (%)	12 (43)	8 (29)	6 (21)	—	48 (36)	15 (11)	7 (5)	—
Hypoalbuminemia (%)	1 (4)	1 (4)	—	—	1 (1)	1 (1)	—	—
Constipation (%)	12 (43)	—	—	—	16 (12)	—	—	—
Stomatitis/mucositis (%)	10 (36)	1 (4)	3 (11)	—	19 (14)	2 (1.5)	3 (2)	—
Erythema (%)	2 (7)	—	1 (4)	—	2 (1.5)	—	1 (1)	—
Asthenia (%)	9 (32)	11 (39)	3 (11)	—	30 (22)	23 (17)	3 (2)	—
Neurotoxicity (%)	21 (75)	4 (14)	—	—	72 (54)	4 (3)	—	—
Hypertension (%)	7 (25)	3 (11)	—	—	11 (8)	3 (2)	—	—
Hypotension (%)	1 (4)	—	—	—	1 (1)	—	—	—
Hematuria (%)	—	1 (4)	—	—	—	1 (1)	—	—
Gingival recession/gingivitis (%)	5 (18)	—	—	—	6 (4)	—	—	—
Rhinitis (%)	22 (78)	—	—	—	50 (37)	—	—	—
Epistaxis (%)	20 (71)	—	—	—	46 (34)	—	—	—
HFS (%)	—	—	—	—	—	—	—	—
Headache (%)	5 (18)	—	—	—	7 (5)	—	—	—
Hypokalemia (%)	2 (7)	—	—	—	2 (1.5)	—	—	—
Hypertransaminasemy (%)	3 (11)	1 (4)	—	1 (4)	5 (4)	2 (1.5)	—	1 (1)
Hyperpigmentation (%)	3 (11)	—	—	—	5 (4)	—	—	—
Fever without infection (%)	6 (21)	—	—	—	6 (4)	—	—	—
Alopecia (%)	3 (11)	7 (25)	3 (11)	—	8 (6)	14 (10)	7 (5)	—
Anemia (%)	3 (11)	2 (7)	—	—	7 (5)	2 (1.5)	—	—
Leucopenia (%)	10 (36)	11 (39)	—	—	34 (25)	17 (13)	—	—
Neutropenia (%)	4 (14)	11 (39)	3 (11)	—	25 (19)	25 (19)	3 (2)	—
Thrombocytopeny (%)	4 (14)	1 (4)	—	—	6 (4)	1 (1)	—	—

TABLE 4: Limiting toxicity syndromes (LTS): overall and in young-elderly patients.

	Overall		Young-elderly		Non-elderly	
	No.	%	No.	%	No.	%
Patients	67	100	28	42	39	58
Limiting toxicity syndromes (LTS)	32	48	13	46	19	49
LTS single site (LTS-ss)	10	15	2	7	8	21
LTS multiple sites (LTS-ms)	22	33	11	39	11	28
Single LT plus G2-3	15	22	9	32	6	15
Double LTs	7	10	2	7	5	13

LT: limiting toxicity; G: grade.

1; G3 stomatitis/mucositis and G2 asthenia, 1; G2 neutropenia for >2 weeks with G2 nausea, 1; and G3 asthenia, 1.

4.4. Activity and Efficacy according to KRAS Genotype and Extension of Metastatic Disease. Among 7 L-L patients, ORR was 86% (α 0.05, CI \pm 28) (see Supplementary material, Table 4, which describes activity, efficacy, and effectiveness of FIr-B/FOx regimen according to KRAS genotype and extension

of metastatic disease); 3 performed liver metastasectomies (43%) and 3 cCRs (43%) in patients who did not undergo liver surgery and showed PFS of 78+, 69+, and 49+ months; median PFS was 30 months (3–78+ months); median OS was not reached (20–78+ months) at a median follow-up of 49 months. Among 19 evaluable O/MM patients, ORR was 84% (α 0.05, CI \pm 17); median PFS was 11 months (4–18 months); median OS was 19 months (6–59 months). Overall, clinical outcome (PFS and OS) in L-L compared to

O/MM patients was significantly different (Figures 1(e) and 1(f)): among *KRAS* wild-type (see Supplementary material, Figure 1(a), which reports PFS and OS of *KRAS* wild-type patients, L-L versus O/MM), P 0.058 for PFS and P 0.035 for OS; among *KRAS* mutant (see Supplementary material, Figure 1(b), which reports PFS and OS of *KRAS* mutant patients, L-L versus O/MM), not significantly different.

5. Discussion

First line medical treatment of MCRC patients consists of triplet regimens including chemotherapeutic drugs, or doublets plus BEV, or doublets plus EGFR-inhibitors in *KRAS* wild-type patients, showing ORR 39%–68%, PFS 7.2–10.6 months, and OS 19.9–26.1 months [2, 4, 7, 8]. Triplet FOLFOXIRI regimen gained ORR 60%, PFS 9.8 months, and OS 23.4 months, and recently showed 5 years-PFS 5% and 5 years-OS 15% [7]. More intensive regimens, consisting of triplet chemotherapy plus targeted agents, can further increase activity, efficacy, and effectiveness of liver metastasectomies [1, 38, 39]. Phase II studies, by Masi et al. [38], and by our group [1], proposed BEV addition to triplet chemotherapy, according to FOLFOXIRI/BEV or FIr-B/FOx schedules, reaching ORR 77% and 82%, liver metastasectomies 40% and 54% in L-L disease, median PFS 13.1 and 12 months, and median OS 30.9 and 28 months. Present retrospective analysis showed that young-elderly patients represented 42% of MCRC patients treated with FIr-B/FOx intensive regimen, mainly characterised by performance status 0 (89%) and intermediate CIRS (93%) stage and confirmed high activity and efficacy (ORR 79%, PFS 11 months, and OS 21 months), as reported in overall MCRC patients [1].

Retrospective analysis of doublets CPT-11, or OXP, associated to 5-FU or capecitabine in older patients reported ORR 18–59.4%, PFS 4.9–10.0 months, and OS 8.5–20.7 months [13–20, 29, 40]. The addition of BEV to 5-FU-based chemotherapy in elderly patients significantly increased PFS 9.2–9.3 and OS 17.4–19.3 months [22, 23]. Triplet chemotherapy or doublet plus BEV obtained ORR 34.9–45.9%, PFS 7.9–9.3 months, and OS 17.4–20.5 months [23–25]. In the HORG-FOLFOXIRI trial, no different clinical outcome was observed in elderly patients; significantly lower PFS and OS were reported in patients with performance status 2 [28, 29]. Liver metastasectomies were reported in 1.3% and 4.2% patients treated with FOLFIRI and FOLFOXIRI, respectively, [29] and can achieve OS 43 months, not significantly different from younger patients [41]. Morbidity and/or mortality after liver surgery were significantly higher in elderly patients (8%) [42]. Our present retrospective data show that intensive FIr-B/FOx treatment of young-elderly MCRC patients, carefully selected according to comorbidity and functional status, may achieve increased activity and clinical outcome than that reported. The high activity is correlated with 18% liver resection rate, 37.5% in L-L patients, and 40% pathologic CR, without increased morbidity and/or mortality.

FOLFOXIRI plus BEV and FIr-B/FOx schedules may increase activity and efficacy in patients with *KRAS* wild-type and mutant genotypes [5, 38]. Median OS of patients treated with FIr-B/FOx was different in *KRAS* wild-type and mutant patients (38 months and 21 months, resp.), but not significantly different [5]. Similarly, FIr-B/FOx clinical outcome was not significantly different according to *KRAS* genotype, in young-elderly patients. Our previous reports of significantly different clinical outcome of L-L compared to multiple metastatic disease [3], particularly in *KRAS* wild-type patients, while not in *KRAS* mutant [5], were confirmed in young-elderly patients and should be prospectively verified.

FIr-B/FOx in young-elderly patients was feasible at median rDI 80%. Cumulative G3–4 toxicities were prevalently represented by diarrhea (21%), stomatitis/mucositis (11%), asthenia (11%), and neutropenia (11%). Individual LTS were reported in 46% young elderly patients, mainly including diarrhea (69.2%), and significantly more represented by LTS-ms compared to LTS-ss (chi-square 3.832, $P = 0.05$), with respect to non-elderly patients. Published studies showed that grade 3/4 toxicities were not significantly different in elderly patients treated with 5-FU or CPT-11 [14–16], slightly increased with FOLFOX [19], and significantly increased by capecitabine (40%), while not by the addition of OXP [20]. Limiting diarrhea was significantly higher with FOLFIRI and FOLFOXIRI [28, 29]. Performance status 2 was significantly associated with increased grade 3/4 neutropenia, febrile neutropenia, diarrhea, and fatigue, compared with performance status 0–1 [28, 29, 40]. In elderly patients, BEV addition to chemotherapy was significantly associated with increased arterial thromboembolism [43], while not to other adverse events [22–25]. The present retrospective, exploratory analysis in a small cohort of MCRC patients, showed that intensive FIr-B/FOx schedule is equivalently safe and feasible, without severe adverse events related to BEV, in young-elderly patients, selected by favourable performance status and functional and comorbidity status, with a rate of LTS-ms significantly increased compared to LTS-ss, with respect to non-elderly patients. Young-elderly MCRC patients suitable for FIr-B/FOx intensive treatment should be carefully selected based on comorbidity and functional status and monitored for individual safety in clinical practice.

6. Conclusions

In fit young-elderly patients, FIr-B/FOx intensive regimen is safe, with toxicity characterized by LTS-ms, high activity, efficacy, and liver metastasectomies, particularly in L-L, *KRAS* wild-type, compared to O/MM. Present findings would be prospectively verified in a larger cohort of young-elderly MCRC patients.

Conflict of Interests

The authors declare that they have no conflict of interests.

Funding

Gemma Bruera is a Ph.D. student in Biotechnology, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, funded by the University of L'Aquila, Italy.

Acknowledgments

The authors thank Gino Coletti and Antonella Dal Mas, Pathology Department, S. Salvatore Hospital, L'Aquila, Italy, for collection and assembly of biological materials. They also thank Daniela Di Giacomo, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, for contribution to molecular genetic analysis.

References

- [1] G. Bruera, A. Santomaggio, K. Cannita et al., "“Poker” association of weekly alternating 5-fluorouracil, irinotecan, bevacizumab and oxaliplatin (FIR-B/FOx) in first line treatment of metastatic colorectal cancer: a phase II study," *BMC Cancer*, vol. 10, article 567, 2010.
- [2] G. Bruera and E. Ricevuto, "Intensive chemotherapy of metastatic colorectal cancer: weighing between safety and clinical efficacy. Evaluation of Masi G, Loupakis F, Salvatore L, et al. Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. *Lancet Oncol* 2010;11:845–52," *Expert Opinion on Biologcal Therapy*, vol. 11, no. 6, pp. 821–824, 2011.
- [3] G. Bruera, K. Cannita, F. Giuliani et al., "Effectiveness of liver metastasectomies in patients with metastatic colorectal cancer treated with FIR-B/FOx triplet chemotherapy plus bevacizumab," *Clinical Colorectal Cancer*, vol. 11, no. 2, pp. 119–126, 2012.
- [4] C. Ficorella, G. Bruera, K. Cannita et al., "Triplet chemotherapy in patients with metastatic colorectal cancer: toward the best way to safely administer a highly active regimen in clinical practice," *Clinical Colorectal Cancer*, vol. 11, no. 4, pp. 229–237, 2012.
- [5] G. Bruera, K. Cannita, D. Di Giacomo et al., "Prognostic value of KRAS genotype in metastatic colorectal cancer (MCRC) patients treated with intensive triplet chemotherapy plus bevacizumab (FIR-B/FOx) according to extension of metastatic disease," *BMC Medicine*, vol. 10, no. 1, article 135, 2012.
- [6] G. Bruera, K. Cannita, A. V. Giordano, R. Vicentini, C. Ficorella, and E. Ricevuto, "Differential prognosis of metastatic colorectal cancer patients post-progression to first line triplet chemotherapy plus bevacizumab, FIR-B/FOx, according to second line treatment and KRAS genotype," *International Journal of Oncology*. In press.
- [7] G. Masi, E. Vasile, F. Loupakis et al., "Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis," *Journal of the National Cancer Institute*, vol. 103, no. 1, pp. 21–30, 2011.
- [8] H. J. Schmoll, E. Van Cutsem, A. Stein et al., "ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making," *Annals of Oncology*, vol. 23, pp. 2479–2516, 2012.
- [9] A. G. Pallis, D. Papamichael, R. Audisio et al., "EORTC Elderly Task Force experts' opinion for the treatment of colon cancer in older patients," *Cancer Treatment Reviews*, vol. 36, no. 1, pp. 83–90, 2010.
- [10] D. Papamichael, R. Audisio, J.-C. Horiot et al., "Treatment of the elderly colorectal cancer patient: SIOG expert recommendations," *Annals of Oncology*, vol. 20, no. 1, pp. 5–16, 2009.
- [11] R. A. Audisio and D. Papamichael, "Treatment of colorectal cancer in older patients," *Nature Reviews Gastroenterology & Hepatology*, vol. 9, no. 12, pp. 716–725, 2012.
- [12] M. Extermann, J. Overcash, G. H. Lyman, J. Parr, and L. Balducci, "Comorbidity and functional status are independent in older cancer patients," *Journal of Clinical Oncology*, vol. 16, no. 4, pp. 1582–1587, 1998.
- [13] G. Folprecht, D. Cunningham, P. Ross et al., "Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials," *Annals of Oncology*, vol. 15, no. 9, pp. 1330–1338, 2004.
- [14] R. A. Popescu, A. Norman, P. J. Ross, B. Parikh, and D. Cunningham, "Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 years or older," *Journal of Clinical Oncology*, vol. 17, no. 8, pp. 2412–2418, 1999.
- [15] S. Chiara, M. T. Nobile, M. Vincenti et al., "Advanced colorectal cancer in the elderly: results of consecutive trials with 5-fluorouracil-based chemotherapy," *Cancer Chemotherapy and Pharmacology*, vol. 42, no. 4, pp. 336–340, 1998.
- [16] G. Folprecht, M. T. Seymour, L. Saltz et al., "Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials," *Journal of Clinical Oncology*, vol. 26, no. 9, pp. 1443–1451, 2008.
- [17] E. Mitry, J.-Y. Douillard, E. Van Cutsem et al., "Predictive factors of survival in patients with advanced colorectal cancer: an individual data analysis of 602 patients included in irinotecan phase III trials," *Annals of Oncology*, vol. 15, no. 7, pp. 1013–1017, 2004.
- [18] R. M. Goldberg, I. Tabah-Fisch, H. Bleiberg et al., "Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer," *Journal of Clinical Oncology*, vol. 24, no. 25, pp. 4085–4091, 2006.
- [19] A. Figer, N. Perez-Staub, E. Carola et al., "FOLFOX in patients aged between 76 and 80 years with metastatic colorectal cancer: an exploratory cohort of the OPTIMOXI study," *Cancer*, vol. 110, no. 12, pp. 2666–2671, 2007.
- [20] M. T. Seymour, L. C. Thompson, H. S. Wasan et al., "Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial," *The Lancet*, vol. 377, no. 9779, pp. 1749–1759, 2011.
- [21] H. Hurwitz, L. Fehrenbacher, W. Novotny et al., "Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer," *The New England Journal of Medicine*, vol. 350, no. 23, pp. 2335–2342, 2004.
- [22] F. F. Kabbinavar, H. I. Hurwitz, J. Yi, S. Sarkar, and O. Rosen, "Addition of bevacizumab to fluorouracil-based first-line treatment of metastatic colorectal cancer: pooled analysis of cohorts of older patients from two randomized clinical trials," *Journal of Clinical Oncology*, vol. 27, no. 2, pp. 199–205, 2009.
- [23] J. Cassidy, L. B. Saltz, B. J. Giantonio, F. F. Kabbinavar, H. I. Hurwitz, and U.-P. Rohr, "Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of

- four randomized studies,” *Journal of Cancer Research and Clinical Oncology*, vol. 136, no. 5, pp. 737–743, 2010.
- [24] M. F. Kozloff, J. Berlin, P. J. Flynn et al., “Clinical outcomes in elderly patients with metastatic colorectal cancer receiving bevacizumab and chemotherapy: results from the BRiTE observational cohort study,” *Oncology*, vol. 78, no. 5-6, pp. 329–339, 2010.
- [25] E. Van Cutsem, F. Rivera, S. Berry et al., “Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study,” *Annals of Oncology*, vol. 20, no. 11, pp. 1842–1847, 2009.
- [26] J. A. Meyerhardt, N. Jackson McCleary, D. Niedzwiecki et al., “Impact of age and comorbidities on treatment effect, tolerance, and toxicity in metastatic colorectal cancer (mCRC) patients treated on CALGB, 80203,” *Journal of Clinical Oncology*, vol. 27, 15s (supplement, abstr 4038), 2009.
- [27] J.-Y. Douillard, S. Siena, J. Cassidy et al., “Randomized, Phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) Versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study,” *Journal of Clinical Oncology*, vol. 28, no. 31, pp. 4697–4705, 2010.
- [28] J. Souglakos, N. Androulakis, K. Syrigos et al., “FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG),” *British Journal of Cancer*, vol. 94, no. 6, pp. 798–805, 2006.
- [29] L. Vamvakas, A. Athanasiadis, A. Karampeazis et al., “Clinical outcome of elderly patients with metastatic colorectal cancer treated with FOLFOXIRI versus FOLFIRI: subgroup analysis of a randomized phase III trial from the Hellenic Oncology Research Group (HORG),” *Critical Reviews in Oncology/Hematology*, vol. 76, no. 1, pp. 61–70, 2010.
- [30] C. Ficorella, E. Ricevuto, M. F. Morelli et al., “Increased tolerability of bimonthly 12-hour timed flat infusion 5-fluorouracil/irinotecan regimen in advanced colorectal cancer: a dose-finding study,” *Oncology Reports*, vol. 15, no. 5, pp. 1345–1350, 2006.
- [31] M. F. Morelli, A. Santomaggio, E. Ricevuto et al., “Triplet schedule of weekly 5-Fluorouracil and alternating irinotecan or oxaliplatin in advanced colorectal cancer: a dose-finding and phase II study,” *Oncology Reports*, vol. 23, no. 6, pp. 1635–1640, 2010.
- [32] F. Di Fiore, F. Blanchard, F. Charbonnier et al., “Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy,” *British Journal of Cancer*, vol. 96, no. 8, pp. 1166–1169, 2007.
- [33] A. Lamy, F. Blanchard, F. Le Pessot et al., “Metastatic colorectal cancer KRAS genotyping in routine practice: results and pitfalls,” *Modern Pathology*, vol. 24, no. 8, pp. 1090–1100, 2011.
- [34] N. Mantel, “Chi-square tests with one degree of freedom: extensions of the Mendel-Haenszel procedure,” *Journal of the American Statistical Association*, vol. 58, pp. 690–700, 1963.
- [35] P. Therasse, S. G. Arbuck, E. A. Eisenhauer et al., “New guidelines to evaluate the response to treatment in solid tumors,” *Journal of the National Cancer Institute*, vol. 92, no. 3, pp. 205–216, 2000.
- [36] E. L. Kaplan and P. Meier, “Nonparametric estimation of incomplete observations,” *Journal of the American Statistical Association*, vol. 53, pp. 457–481, 1958.
- [37] R. Peto and J. Peto, “Asymptotically efficient rank invariant test procedures,” *Journal of the Royal Statistical Society A*, vol. 135, pp. 185–206, 1972.
- [38] G. Masi, F. Loupakis, L. Salvatore et al., “Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial,” *The Lancet Oncology*, vol. 11, no. 9, pp. 845–852, 2010.
- [39] C. Garufi, A. Torsello, S. Tumolo et al., “Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial,” *British Journal of Cancer*, vol. 103, no. 10, pp. 1542–1547, 2010.
- [40] D. J. Sargent, C. H. Köhne, H. K. Sanoff et al., “Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer,” *Journal of Clinical Oncology*, vol. 27, no. 12, pp. 1948–1955, 2009.
- [41] R. Adam, A. Frilling, D. Elias et al., “Liver resection of colorectal metastases in elderly patients,” *British Journal of Surgery*, vol. 97, no. 3, pp. 366–376, 2010.
- [42] J. Figueras, E. Ramos, S. López-Ben et al., “Surgical treatment of liver metastases from colorectal carcinoma in elderly patients. When is it worthwhile?” *Clinical and Translational Oncology*, vol. 9, no. 6, pp. 392–400, 2007.
- [43] F. A. Scappaticci, J. R. Skillings, S. N. Holden et al., “Arterial thromboembolic events and patients with metastatic carcinoma treated with chemotherapy and bevacizumab,” *Journal of the National Cancer Institute*, vol. 99, pp. 1232–1239, 2007.



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

