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Clinical Studies

A triplet combination with irinotecan (CPT-11), oxaliplatin (LOHP), continuous infusion 5-fluorouracil and leucovorin (FOLFOXIRI) plus cetuximab as first-line treatment in *KRAS* wt, metastatic colorectal cancer: a pilot phase II trial

Z Saridaki[1], N Androulakis[2], N Vardakis[2], L Vamvakas[2], E Kabouraki[2], K Kalbakis[2], D Hatzidaki[2], A Voutsina[1], D Mavroudis[1,2], V Georgoulias[1,2] and J Souglakos[*,1,2]

[1]Laboratory of Tumor Cell Biology School of Medicine, University of Crete, Heraklion, Greece; [2]Department of Medical Oncology, University Hospital of Heraklion, Voutes and Stavrakia, PO BOX 1352, Heraklion, Crete 71110, Greece

BACKGROUND: We conducted an open-label, pilot phase II trial to evaluate the efficacy and safety of FOLFOXIRI plus cetuximab as first-line treatment of patients with metastatic colorectal cancer (mCRC).

METHODS: Thirty patients with *KRAS* wild-type mCRC, <70 years and with performance status 0–1 were included in the trial.

RESULTS: Complete and partial responses were observed in 4 (13.3%) and 17 (56.7%) patients, respectively (overall response rate (ORR) = 70%; 95% confidence interval (CI): 53.6%-86.4%); 8 patients (26.7%) had stable disease and 1 had progressive disease. The median time to tumour progression was 10.2 months (95% CI: 7.1–13.4) and the overall median survival time was 30.3 months (95% CI: 18.8–41.9). Secondary R0 resection was performed in 11 (37%) patients. Grade 3 or 4 diarrhoea and neutropenia were observed in 16 (53%) and 7 (23.3%) patients, respectively, and febrile neutropenia observed in 2 (6.6%) patients. Neurotoxicity grade 2 or 3 was reported in 7 (23.3%) and in 2 (6.7%) patients, respectively, and grade 3 rush was reported in 1 patient.

CONCLUSION: The FOLFOXIRI/cetuximab combination presented increased activity in terms of response rate and R0 secondary liver metastases resection, and merits further investigation, especially in patients with initially unresectable disease confined to the liver.

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Colorectal cancer (CRC) remains a major health problem with an estimated 143 397 new cases and 51 690 deaths occurring in 2012 in the United States alone (Siegel *et al*, 2012). Despite the progress made in the management of metastatic CRC (mCRC) over the last few years, with the incorporation in combination chemotherapy of two monoclonal antibodies targeting the epidermal growth factor receptor (Cunningham *et al*, 2004; Saltz *et al*, 2004; Van Cutsem *et al*, 2007) and the vascular endothelial growth factor (Hurwitz *et al*, 2004), the provided clinical benefit is modest and their long-term outcome is still unsatisfactory.

The upfront administration of all active chemotherapeutic agents (the FOLFOXIRI regimen) has been tested, and its efficacy and tolerability was evaluated in two phase II studies, where the documented resectability rate (RR) was 58% and 69%, the time to tumour progression (TTP) was 13 and 10.4 months, and the overall survival (OS) 22.5 and 26.5 months, respectively (Falcone *et al*, 2002; Souglakos *et al*, 2002). In continuation, the same Greek and Italian groups, tested the FOLFOXIRI *vs* the FOLFIRI in two randomised trials (Souglakos *et al*, 2006; Falcone *et al*, 2007). Although the Italian study reported that FOLFOXIRI regimen was superior in terms of RR, progression-free survival (PFS) and OS (Falcone *et al*, 2007), this could not be demonstrated in the Greek trial (Souglakos *et al*, 2006). This discrepancy in the results of the two trials may be attributed to the different schedule and doses, differences in the inclusion criteria, as well as in the difference of OS in the control arm (19.5 and 16.7 months in the HORG and GONO, respectively). Conversely, it was demonstrated that FOLFOXIRI was associated with a higher resectability rate compared with FOLFIRI (Souglakos *et al*, 2006). In addition, the regimen was found to be more toxic for patients with performance status (PS) 2 and those aged >65 years. Furthermore, in the young patients (65 years) FOLFOXIRI was found to be statistically significantly superior (RR 52.5% *vs* 32%) and with a favourable toxicity profile (Vamvakas *et al*, 2010). The common finding of the two trials was that FOLFOXIRI significantly increase the R0 secondary resections, which were triple in both trials: from 4 to 12% in the HORG trial and from 12 to 36% in the GONO trial (Falcone *et al*, 2007).

The addition of cetuximab to either FOLFIRI or FOLFOX led to an increased R0 secondary resection rate in *KRAS* wild-type patients, as it has been demonstrated in the randomised phase III CRYSTAL and phase II (OPUS) trials (Bokemeyer *et al*, 2009; Van Cutsem *et al*, 2009). On the basis of the above mentioned background, we conducted a non-randomised, open-label, pilot

*Correspondence: Dr J Souglakos;
E-mail: johnsougl@gmail.com
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phase II clinical trial to evaluate the activity and safety of FOLFOXIRI in combination with cetuximab as first-line treatment in young patients (<70 years old) with good PS (0–1) and unresectable mCRC.

MATERIALS AND METHODS

Patients and eligibility criteria

The study was open for patients' enrolment from January 2007 to August 2010. Patients with histologically proven, *KRAS* wild-type unresectable mCRC, who have not previously received chemotherapy for metastatic disease, were eligible for the trial. Patients who had received adjuvant chemotherapy were eligible if they have remained free of disease for at least 6 months after the completion of adjuvant therapy. Other eligibility criteria were: age 18–70 years; PS (Eastern Cooperative Oncology Group) 0–1; at least one measurable lesion according to RECIST criteria; adequate haematologic parameters (absolute neutrophil count $\geqslant 1.5 \times 10^9$ per l and platelets $\geqslant 100 \times 10^9$ per l); creatinine and total bilirubin <1.25 times the upper limit of normal (UNL); aspartate and alanine aminotransferase <3.0 times the (UNL; <5 times in case of liver metastases existence); absence of active infection or malnutrition (loss of more than 20% of the body weight); and no history of a second primary tumour.

The protocol was approved by the ethics and scientific institutional and national committees. Patients were informed of the investigational nature of the study and provided their written informed consent before registration and participation.

Chemotherapy

Cetuximab was administered at a dose of $500\,mg\,m^{-2}$ as a 2-h infusion on day 1 after pre-medication with histamine receptor antagonist and at least 1 h before the administration of chemotherapy. The administration of cetuximab every 2 weeks was based on previous reports, which supported the functional equivalence of the weekly and the every second week schedule (Tabernero *et al*, 2010). The FOLFOXIRI regimen was administered as previously described: irinotecan was administered at the dose of $150\,mg\,m^{-2}$ as a 30-min i.v. infusion on day 1; LV was given at the dose of $200\,mg\,m^{-2}$ as a 2-h i.v. infusion, followed by 5-fluorouracil (5-FU) $400\,mg\,m^{-2}$ as i.v. bolus, and then $600\,mg\,m^{-2}$ as a 22-h continuous i.v. infusion, on days 2 and 3; oxaliplatin was administered on day 2 at the dose of $65\,mg\,m^{-2}$ as a 2-h i.v. infusion in parallel with LV, but using different lines (Souglakos *et al*, 2006). Treatment was administered every 2 weeks until disease progression or unacceptable toxicity, or until the patient declined further treatment. Cetuximab was continued until disease progression or unacceptable toxicity, even if chemotherapy had to be prematurely discontinued, or until the patient declined further treatment. For patients who were submitted to a secondary resection, a total of 6 months (12 cycles) of treatment was administered peri-operatively.

Patients were assessed for toxicity before each cycle of chemotherapy using the US National Cancer Institute's – Common Toxicity Criteria, Version 3.0. Especially for cetuximab, if a patient experienced grade 3 skin toxicity, cetuximab therapy was delayed for up to two consecutive infusions without changing the dose level. If the toxicity resolved to grade 2 or less, treatment was resumed. In the case of a second occurrence of grade 3 skin toxicity, cetuximab therapy was delayed for up to two consecutive infusions with concomitant dose reductions to 400 and $300\,mg\,m^{-2}$, respectively, which were permanent until completion of treatment. Cetuximab treatment was discontinued and the patient was withdrawn from the study if more than two consecutive infusions were withheld or if a fourth occurrence of grade 3 skin toxicity occurred despite appropriate dose reduction. Cetuximab therapy was not withheld for chemotherapy-related toxicities.

In case of allergic/hypersensitivity reactions, appropriate treatment measures were performed. Once the cetuximab infusion rate was decreased due to an allergic/hypersensitivity reaction, it remained decreased for all subsequent infusions. In case of a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion was stopped and the subject was removed from the study. In case of grade 3 or 4 allergic/hypersensitivity reactions at any time, cetuximab was discontinued.

Chemotherapy was delayed until recovery if neutrophils were less than 1.5×10^9 per l or platelets less than 100×10^9 per l, or for significant persisting non-haematologic toxicity. Doses of all chemotherapy agents were reduced by 15% in subsequent cycles in case of grade 4 neutropenia, or grade 3–4 thrombocytopenia lasting for more than 3 days, or in case of febrile neutropenia. Irinotecan and 5-FU doses were reduced by 15% in subsequent cycles in case of grade 3–4 diarrhoea. The 5-FU dose was reduced in grade 3–4 stomatitis or dermatitis. Oxaliplatin dose was reduced by 15% in case of persistent ($\geqslant$14 days) paraesthesia or temporary (7–14 days) painful paraesthesia, or functional impairment. In cases of persistent ($\geqslant$14 days) painful paraesthesia or functional impairment, oxaliplatin was omitted in subsequent cycles from the regimen until full patient recovery.

Patient evaluation

Pretreatment evaluation included medical history and physical examination, complete blood cell count with differential and platelet count, whole blood chemistry, determination of serum levels of carcinoembryonic antigen and computed tomography scans of the chest and abdomen, and had to be performed within 2 weeks before study entry. *KRAS* codon 12 and 13 mutations were analysed, at the time of patient's registration, in microdissected samples from the primary tumour by standard Sanger sequencing as previously described (Saridaki *et al*, 2011). During treatment, a complete blood cell count with differential and platelet count was performed weekly, and in cases of grade 3–4 neutropenia, thrombocytopenia, or febrile neutropenia, it was performed daily until haematologic recovery. In addition, patients were clinically assessed, and routine biochemical tests were performed before each treatment cycle. Response to treatment was evaluated after four 2-week cycles (8 weeks) or sooner if clinically indicated.

Statistical considerations

The primary endpoint of the trial was the objective response rate (ORR) according to the RECIST criteria (Therasse *et al*, 2000), and the secondary endpoints were R0-RR, TTP, median OS (mOS), toxicity profile and pharmacogenomic analysis.

The study was designed as an exploratory, pilot, phase II study. We considered that if a response rate (complete and partial response) was observed in at least 60% (95% confidence interval (CI): 50.82–75.18%) in 30 patients with wild-type KRAS, the regimen would merit further evaluation in prospective subsequent trials. The normal approximation method was used for the calculation of 95% CI. In addition, if one of the first 6 patients, receiving at least 70–80% of the planned doses died because of toxicity, the study would be discontinued, and depending on the reason of toxic death the protocol would be amended or permanently discontinued. The analysis of the primary endpoint was performed in the intent-to-treat population, defined as all patients who have been enroled to the study.

Because of the exploratory nature of the study, mainly descriptive statistics were scheduled to be used. The probability of survival was estimated by the Kaplan–Meier method and the CIs were calculated using methods for exact binomial CIs.

Response duration was measured from the first documentation of response to disease progression. The TTP was determined as the interval between treatment initiation and the date when disease progression was first documented. Survival was measured from the date of registration to date of death. The follow-up time was measured from the day of first treatment administration to the last contact or death.

RESULTS

Patients characteristics

The patients' characteristics and demographics are summarised in Table 1. The median age was 64 years (range, 36–70 years), 27 (90%) of the patients had a PS of 0, and the median number of target lesions was 1 per patient. Eighty per cent of the enroled patients had received prior 5-FU-based adjuvant chemotherapy. The median time elapsed between the first diagnosis of metastases and study entry was 1.5 month (range, 0.4–2.0 months). All patients were evaluable for toxicity, and all, but one, were evaluable for response to treatment due to sudden death possibly related to treatment, and in the intent-to-treat analysis she was considered as having progressive disease.

Table 1 Patients' characteristics

	No of patients	%
Number of patients enroled	30	
Number of patients evaluable for toxicity	30	
Number of patients evaluable for response	29	
Age		
Median (range)	64 (36–70)	
Sex		
Male	14	46.7
Female	16	53.3
Performance status (WHO)		
0	27	90
1	3	10
Primary tumour location		
Colon	22	73.3
Rectal	8	26.7
Prior surgery		
Yes	24	80
No	6	20
Prior adjuvant chemotherapy		
Yes	24	80
No	6	20
Prior adjuvant RT		
Yes	4	13.3
No	26	86.7
Disease involved sites		
Loco-regional	2	6.7
Liver	25	83.3
Lymph nodes	10	33.3
Lung	6	20
Peritoneum	2	6.7
Other	5	16.7
Number of organs involved		
1	17	56.7
2	8	26.7
3	3	10
4	2	6.7

Treatment efficacy

In an intent-to-treat analysis, documented complete and partial response were observed in 4 (13.3%) and 17 (56.7%) patients, respectively (overall response rate (ORR) = 70%; 95% CI: 53.6–86.4%). In addition, 8 patients (26.7%) had stable disease and 1 had progressive disease. The median time to initial documentation of response was 2 months (range, 2.0–34.0 months). The median duration of response was 7 months (range, 0.5–33.1 months; 95% CI: 5.5–8.5) and the median TTP was 10.2 months (range, 0.2–38.6 months; 95% CI: 7.1–13.4). After a median follow-up period of 31 months (range, 0.2–45.5), the overall median survival time was 30.3 months (95% CI: 18.8–41.9).

All patients included in the study had unresectable metastatic disease according to their treating physician and the evaluation of the surgeons in the University hospital of Heraklion. Sixteen of those patients presented metastatic disease confounded to the liver, and the disease was unresectable due to extend to $>60\%$ of the liver parenchyma (11 patients) or technical reasons (5 patients). Secondary R0 resection was performed in 11 (37%) of these patients, 10 with lesions in the liver and 1 with lung metastasis (Table 2) without significant morbidity or mortality. Especially for patients with disease limited to the liver ($n = 16$), R0 resections were achieved in 10 patients, leading to an R0-RR of 62%. Five of the 11 patients with an R0 resection have relapsed after a median time of 10.2 months (range, 7–14.6 months) post-metastasectomy; after a median follow-up of 26 months (range, 13–37), all metastasectomised patients were alive at the time of analysis (Table 2). The resection was performed after four or eight treatment cycles in four and seven patients, respectively. Treatment was continued with the combination afterwards until the completion of 12 of the peri-operative treatment in all cases.

Treatment toxicity

The toxicity profile of the regimen is presented in Table 3. Diarrhoea and anaemia were the most common toxicities of the combination observed in 90% and 80% of the patients, respectively, followed by neutropenia (50%), fatigue (46.7%) and stomatitis (43.4%). Severe, grade 3 or 4 diarrhoea was observed in 16 (53%) patients. In most patients, anaemia was of grade 1 (43.3%) and 2 (33.3%). Grade 3 and 4 neutropenia was documented in 6 (20%) and 1 (3.3%) patients, respectively, whereas febrile neutropenia of grade 2 and grade 4 was developed in 2 patients (6.6%), each one requiring hospitalisation and i.v. antibiotics. Neurosensory toxicity was observed in 9 patients (30%). Cold-induced dysaesthesia was reported in 7 patients (23.3%) and paraesthesia without pain in 2 (6.7%). Grade 3 rash was observed only in 1 patient (3.3%), whereas grade 1 and 2 in 10 patients (26.6%). Hypersensitivity reactions were observed in 9

Table 2 Characteristics of patients who underwent secondary resection

	Metastatic site	Response	Relapse	TTP (months)	Survival (months)
Patient 1	Liver	CR	No	36.8	36.8
Patient 2	Liver	PR	Yes	14.6	28.9
Patient 3	Liver	PR	No	25.6	25.6
Patient 4	Liver	PR	Yes	8.2	25.6
Patient 5	Liver	PR	No	20.8	20.8
Patient 6	Liver	CR	No	34.8	34.8
Patient 7	Liver	CR	No	26.9	26.9
Patient 8	Liver	PR	Yes	10.4	27.1
Patient 9	Liver	PR	No	12.4	14.2
Patient 10	Liver	PR	Yes	14.3	26.5
Patient 11	Lung	PR	Yes	7	26

Abbreviations: CR = complete response; PR = partial response; TTP = time to tumour progression.

Table 3 Toxicity of the FOLFOXIRI/erbitux combination in all patients and all cycles

	Grade 1		Grade 2		Grade 3		Grade 4	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Haematologic toxicity								
Neutropenia	3	10.0	5	16.7	6	20.0	1	3.3
Anaemia	13	43.3	10	33.3	1	3.3	—	—
Thrombocytopenia	7	23.3	—	—	—	—	2	6.7
Febrile neutropenia	—	—	1	3.3	—	—	1	3.3
Non-haematologic toxicity								
Nausea	6	20.0	3	10.0	1	3.3	—	—
Vomiting	3	10.0	3	10.0	4	13.3	—	—
Diarrhoea	6	20.0	5	16.7	13	43.3	3	10.0
Stomatitis	5	16.7	5	16.7	3	10.0	—	—
Constipation	3	10.0	—	—	—	—	—	—
Neurotoxicity	7	23.3	2	6.7	—	—	—	—
Allergy	5	16.7	4	13.3	—	—	—	—
Asthenia	8	26.7	6	20.0	—	—	—	—
Hand/Foot	2	6.7	3	10.0	1	3.3	—	—
Rush	6	20.0	4	13.3	1	3.3	—	—

Table 4 Toxicity of the FOLFOXIRI/erbitux combination according to patients' gender

Gender	Male	Female	Male	Female	Male	Female	Male	Female	
No. of patients (N)	(14)	(16)	(12)	(15)	(12)	(15)	(14)	(16)	
	Grade 1	Grade 1	Grade 2	Grade 2	Grade 3	Grade 3	Grade 4	Grade 4	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*P*-value
Haematologic toxicity															
Neutropenia	2	14.3	1	6.3	2	14.3	3	18.8	3	21.4	3	18.8	1	7.1	—	—	0.254
Anaemia	7	50.0	6	37.5	4	28.6	6	37.5	1	7.1	—	—	—	—	—	—	0.641
Thrombocytopenia	3	21.4	4	25.0	—	—	—	—	—	—	—	—	1	7.1	1	6.3	0.508
Febrile neutropenia	—	—	—	—	—	—	1	6.3	—	—	—	—	1	7.1	—	—	0.216
Non-haematologic toxicity															
Nausea	1	7.1	5	31.3	1	7.1	2	12.5	—	—	1	6.3	—	—	—	—	0.091
Vomiting	—	—	3	18.8	—	—	3	18.8	—	—	4	25.0	—	—	—	—	0.032
Diarrhoea	3	21.4	2	18.8	3	21.4	2	12.5	6	42.9	7	43.8	—	—	3	18.8	0.282
Stomatitis	1	7.1	4	25.0	3	21.4	2	12.5	—	—	3	18.8	—	—	—	—	0.108
Constipation	1	7.1	2	12.5	—	—	—	—	—	—	—	—	—	—	—	—	0.567
Neurotoxicity	2	14.3	5	31.3	—	—	2	12.5	—	—	—	—	—	—	—	—	0.047
Allergy	4	28.6	1	6.3	4	28.6	—	—	—	—	—	—	—	—	—	—	0.314
Asthenia	4	28.6	4	25.0	—	—	6	37.5	—	—	—	—	—	—	—	—	0.261
Hand/Foot	—	—	2	12.5	2	14.3	1	6.3	—	—	1	6.3	—	—	—	—	0.497
Rush	3	21.4	3	18.8	2	14.3	2	12.5	—	—	1	6.3	—	—	—	—	0.562

(30%) patients and were, in general, mild. Hand-foot syndrome was detected in 6 patients (20%) but only 1 (3.3%) had grade 3. Four cases of infection were identified throughout the study. Five treatment-related admissions to the hospital were reported, all of them for severe diarrhea, whereas two of them also presented febrile neutropenia. There was one treatment-related death in a patient with disseminated peritoneal carcinomatosis, who developed grade 4 diarrhoea.

The analysis of the toxicity according to the gender revealed that vomiting was observed exclusively in females ($P = 0.032$), and neurotoxicity was more frequent in females ($P = 0.047$) (Table 4).

Compliance with treatment

At the time of this analysis, all 30 patients (100%) have discontinued treatment because of the following reasons: disease progression in 6 patients (20.0%), unacceptable toxicity in 5 patients (16.7%; 1 with grade 4 diarrhoea, 1 with grade 4 thrombocytopenia, 1 sudden death and 2 with an LOHP-related allergic reaction), patient withdrawal in 3 (10.0%), primary tumour surgical removal in 2 (6.7%) and completion of treatment in 14 (46.7%; 11 patients with secondary resection, who completed 6 months of peri-operative treatment, and 3 patients who were under treatment for more than 6 months at the time of study termination). In total, 300 courses of chemotherapy have been administered (median, 12 courses per patient; range 1–16). Seventy one courses were delayed for a median of 7 days (range 3–56) because of haematologic ($n = 12$), non-haematologic ($n = 20$), and both haematologic and non-haematologic toxicity ($n = 9$), and 30 courses were delayed because of reasons unrelated to treatment or diseases. The median interval between cycles was 15 days (range, 15–19). Dose reduction was required in 38 cycles (12.7%) because of haematologic ($n = 4$ cycles; 1.3%) and non-haematologic toxicity ($n = 26$ cycles; 8.7%). Administration of GCSF was required in 36 cycles (12%) for the treatment of severe or febrile neutropenia. The delivered relative dose intensity was 85.3% for CPT-11, 93.2% for LOHP, 83.2% for 5-FU, 94.0% for LV and 94.4% for erbitux of the protocol-planned doses.

DISCUSSION

This is the second study investigating the relevance of cetuximab addition to FOLFOXIRI in the mCRC setting. In the current study the chemotherapy has been administered in fixed standard timeframe for each agent, whereas in the previous study it was administered in a chronomodulated fashion. We show that intensive chemotherapy with FOLFOXIRI plus cetuximab resulted in a particularly high response rate and a RR of 37%. Especially, for patients with liver-limited disease (LLD), which was initially unresectable, the R0-RR was 62%. Furthermore, after a median follow-up period of 31 months, our combination achieved an mOS time of 30.3 months.

Initial promising data demonstrated that cetuximab alone or in combination with irinotecan had clinical activity in irinotecan-refractory CRC patient (Cunningham *et al*, 2004; Saltz *et al*, 2004). Afterwards, the addition of cetuximab to chemotherapy regimens, such as FOLFIRI and FOLFOX, was shown to increase RR, PFS and OS in the first-line setting (Bokemeyer *et al*, 2009; Van Cutsem *et al*, 2009). Furthermore, the addition of cetuximab to the triple combination of CPT-11/L-OHP/5-FU/LV administered under chronomodulation was the subject of the POCHER trial, which was recently published (Garufi *et al*, 2010). In this trial, cetuximab plus the chronomodulated triplet achieved 60% complete respectability of liver metastases (Garufi *et al*, 2010). The FOLFOXIRI regimen has been evaluated with the addition of bevacizumab in another phase II trial where the primary endpoint was the PFS, and bevacizumab was also administered as maintenance treatment (Masi *et al*, 2010). The results were deemed promising in terms of PFS and without the occurrence of unforeseen adverse events (Masi *et al*, 2010). Our results confirm the findings of the POCHER trial (Garufi *et al*, 2010) and extend those of the CELIM trial, in which the addition of cetuximab in either FOLFOX or FOLFIRI was evaluated in the neoadjuvant setting (Folprecht *et al*, 2005). The RR was 37% in the total population and 62% in LLD in the current study, 60% in POCHER trial (Garufi *et al*, 2010) and 38% for FOLFOX/cetuximab, whereas 30% for FOLFIRI/cetuximab in the CELIM trial (Folprecht *et al*, 2005). We documented a complete and partial response rate of 70%, which was 79% in the POCHER trial (Garufi *et al*, 2010), and 68% and 57% in the CELIM's FOLFOX or FOLFIRI–cetuximab combination, respectively (Folprecht *et al*, 2005). Furthermore, the median TTP was 10.2 months in our patients' population, whereas it was 14 months in the POCHER trial (Garufi *et al*, 2010), and the mOS in our study was 30.3 months after a median follow-up period of 31 months, whereas it was 37 months in the POCHER trial (Garufi *et al*, 2010). In addition, other studies have also, provided evidence of the effectiveness of cetuximab addition to a doublet combination in unselected mCRC patients, in terms of PFS and OS (Bokemeyer *et al*, 2009; Van Cutsem *et al*, 2009). In the OPUS and CRYSTAL trials, the addition of cetuximab to FOLFOX or FOLFIRI, respectively, led to increase of liver metastases RR, which was double in the cetuximab arm in both trials (Bokemeyer *et al*, 2009; Van Cutsem *et al*, 2009). In addition, another phase II study reported an impressive RR of 80.9% and an mOS exceeding 2 years (24.7 months; Assenat *et al*, 2011). Finally, the addition of panitumumab to FOLFOXIRI in *KRAS-NRAS-HRAS-BRAF* wild-type patients led to an RR of 89%, indicating that selection of patients based on multiple molecular markers should be evaluated in subsequent trials with this combination (Lonardi *et al*, 2012).

Toxicity was increased in our study with grade 3 or 4 diarrhoea and neutropenia reaching 53.3% and 23.3%, respectively. In the POCHER trial (Garufi *et al*, 2010), grade 3 or 4 diarrhoea was the major treatment toxicity documented in 93% of the patients, whereas similar incidence of diarrhoea was observed in the study of Assenat *et al* (2011). These findings indicate that the addition of cetuximab to three different schedules of FOLFOXIRI increases the incidence and severity of diarrhoea of the triple regimen. Dose reductions and/or modification were frequently required in all three studies, whereas in the POCHER trial an amendment with doses reduction was mandatory for the continuation and completion of the study. In addition, in the current and POCHER trials an increased gastrointestinal and neurosensory toxicity was observed in females. For these reasons, dose or schedule modification may be re-evaluated in future trials. In addition, the use of chronomodulated FOLFOXIRI in the POCHER study limited the administration of this type of chemotherapy in experienced centres with the necessary equipment.

The addition to the triplet combination of a monoclonal antibody, this time bevacizumab, in an unselected patients' population was recently published by Falcone *et al* (Masi *et al*, 2010). The RR was comparable to that of the present study, as well as with the that reported in POCHER trial (Garufi *et al*, 2010). The documented liver metastases RR of 40%, which was in the same rate with what was previously observed with the triplet alone (36%) by the same group, but less compared with ours (62%) and POCHER trial (60%; Garufi *et al*, 2010).

Potential limitations of our study are that it is a single-centre, non-comparative study, with a small number of patients enroled. Contrary, two strong points are, on the one hand the fact that the patients were selected on the basis of molecular markers and partly on physiological factors, as the enroled patients were younger than 70 years of age and with good PS. The benefit of the combination was greater than the potential risk, especially for the patients whose metastases became resectable after treatment, as it was associated with high response rates and facilitated metastasectomies in 37% of the enroled patients, providing promising survival results. In conclusion, the FOLFOXIRI + cetuximab regimen presented interesting results with high response rate and R0 secondary resections in patients <70 years old, with good PS and limited number of target lesions ($\leqslant 2$), and merits further investigation, especially in patients with initially unresectable disease confined to the liver.

Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

Assenat E, Desseigne F, Thezenas S, Viret F, Mineur L, Kramar A, Samalin E, Portales F, Bibeau F, Crapez-Lopez E, Bleuse JP, Ychou M (2011) Cetuximab plus FOLFIRINOX (ERBIRINOX) as first-line treatment for unresectable metastatic colorectal cancer: a phase II trial. *Oncologist* **16**: 1557–1564

Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de BF, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* **27**: 663–671

Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van CE (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* **351**: 337–345

Falcone A, Masi G, Allegrini G, Danesi R, Pfanner E, Brunetti IM, Di PA, Cupini S, Del TM, Conte P (2002) Biweekly chemotherapy with oxaliplatin, irinotecan, infusional Fluorouracil, and leucovorin: a pilot study in patients with metastatic colorectal cancer. *J Clin Oncol* **20**: 4006–4014

Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crino L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S,

Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* **25**: 1670–1676

Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH (2005) Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* **16**: 1311–1319

Garufi C, Torsello A, Tumolo S, Ettorre GM, Zeuli M, Campanella C, Vennarecci G, Mottolese M, Sperduti I, Cognetti F (2010) Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. *Br J Cancer* **103**: 1542–1547

Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* **350**: 2335–2342

Lonardi S, Fornaro L, Bergamo f, Schirripa M, Aprile G, Morvillo M, Masi G, Loupakis F, Calvetti L, Cremolini C, Salvatore L, Zaniboni A, Zagonel V, Falcone A (2012) Phase II study of panitumumab (P) in combination with FOLFOXIRI as first-line treatment of metastatic colorectal cancer (mCRC): Activity in molecularly selected patients (pts). *J Clin Oncol* **30**(suppl.): abstract 3555.

Masi G, Loupakis F, Salvatore L, Fornaro L, Cremolini C, Cupini S, Ciarlo A, Del MF, Cortesi E, Amoroso D, Granetto C, Fontanini G, Sensi E, Lupi C, Andreuccetti M, Falcone A (2010) Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. *Lancet Oncol* **11**: 845–852

Saltz LB, Meropol NJ, Loehrer Sr PJ, Needle MN, Kopit J, Mayer RJ (2004) Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* **22**: 1201–1208

Saridaki Z, Tzardi M, Papadaki C, Sfakianaki M, Pega F, Kalikaki A, Tsakalaki E, Trypaki M, Messaritakis I, Stathopoulos E, Mavroudis D, Georgoulias V, Souglakos J (2011) Impact of KRAS, BRAF, PIK3CA mutations, PTEN, AREG, EREG expression and skin rash in $>/=$ 2 line cetuximab-based therapy of colorectal cancer patients. *PLoS One* **6**: e15980

Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. *CA Cancer J Clin* **62**: 10–29

Souglakos J, Androulakis N, Syrigos K, Polyzos A, Ziras N, Athanasiadis A, Kakolyris S, Tsousis S, Kouroussis C, Vamvakas L, Kalykaki A, Samonis G, Mavroudis D, Georgoulias V (2006) 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). *Br J Cancer* **94**: 798–805

Souglakos J, Mavroudis D, Kakolyris S, Kourousis C, Vardakis N, Androulakis N, Agelaki S, Kalbakis K, Tsetis D, Athanasiadis N, Samonis G, Georgoulias V (2002) Triplet combination with irinotecan plus oxaliplatin plus continuous-infusion fluorouracil and leucovorin as first-line treatment in metastatic colorectal cancer: a multicenter phase II trial. *J Clin Oncol* **20**: 2651–2657

Tabernero J, Cervantes A, Rivera F, Martinelli E, Rojo F, von HA, Macarulla T, Rodriguez-Braun E, Eugenia Vega-Villegas M, Senger S, Ramos FJ, Rosello S, Celik I, Stroh C, Baselga J, Ciardiello F (2010) Pharmacogenomic and pharmacoproteomic studies of cetuximab in metastatic colorectal cancer: biomarker analysis of a phase I dose-escalation study. *J Clin Oncol* **28**: 1181–1189

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van GM, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* **92**: 205–216

Vamvakas L, Athanasiadis A, Karampeazis A, Kakolyris S, Polyzos A, Kouroussis C, Ziras N, Kalbakis K, Georgoulias V, Souglakos J (2010) 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). *Crit Rev Oncol Hematol* **76**: 61–70

Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pinter T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer *N Engl J Med* **360**: 1408–1417

Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon JL, Van Laethem JL, Maurel J, Richardson G, Wolf M, Amado RG (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* **25**: 1658–1664