Overview

The Oncologist®
The official journal of the Society for Translational Oncology

First Published Online November 13, 2013

DOI: 10.1634/theoncologist.2013-0093

Title: Metronomic Capecitabine in Advanced Hepatocellular Carcinoma Patients: A Phase II Study

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Agenzia Italianadel Farmaco Identifier: EudraCT 2008-002299-92

Sponsor(s): Azienda Ospedaliera di Bologna Policlinico Sant'Orsola M. Malpighi (54/2008/U/Sper)

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IRB Approved: Yes

Disclosures:
Rita Golfieri: Honoraria Received: Bayer
Luigi Bolondi: Consultant/Advisory Role: Bayer, BMS; Honoraria Received: Bayer,Esaote, BMS, Bracco; Research Funding/ Contracted Research: Bayer, BMS
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Author Summary: Abstract and Brief Discussion

Background
Antiangiogenic treatment with targeted agents is effective in advanced hepatocellular carcinoma (HCC). This trial evaluated the safety and efficacy of metronomic capecitabine in patients with HCC.

Methods
This single-institution phase II trial included 59 previously untreated patients with advanced HCC and 31 patients resistant to or intolerant of sorafenib. The treatment schedule was capecitabine 500 mg twice daily until progression of disease, unacceptable toxicity level, or withdrawal of informed consent. Progression-free survival (PFS) was chosen as the primary endpoint.

Results
A total of 59 previously untreated and 31 previously treated patients with HCC were enrolled. The first cohort achieved a median PFS of 6.03 months and an overall survival (OS) of 14.47 months. Two patients achieved a complete response, 1 patient achieved partial response, and in 30 patients, stable disease was the best outcome. The second cohort achieved a median PFS of 3.27 months and a median OS of 9.77 months. No complete or partial responses were observed, but 10 patients had stable disease. An unscheduled comparison of the first cohort of patients with 3,027 untreated patients with HCC from the Italian Liver Cancer (ITA.LI.CA) database was performed. One-to-one matching according to demographic/

etiologic/oncologic features was possible for 50 patients. The median OS for these 50 capecitabine-treated patients was 15.6 months, compared with a median OS of 8.0 months for the matched untreated patients ($p = .043$).

Conclusion

Metronomic capecitabine is well tolerated by patients with advanced HCC and appears to have activity both in treatment-naive patients and in those previously treated with sorafenib.

Discussion

In patients treated with first-line metronomic capecitabine, the median progression-free survival , which was our primary outcome measure, was >6 months, much longer than the 2.5 months reported for historical control patients. A median overall survival OS of 14.5 months (Fig. 1) is also encouraging, and interestingly, was not different for the 26 patients classified Barcelona-Clinic Liver Cancer (BCLC)-B and 33 patients classified BCLC-C. Median survival time of previously untreated patients was nearly double that of patients undergoing palliation, who were individually matched from the ITA.LI.CA database (15.6 vs. 8.0 months, respectively) (Fig. 2), providing further support for the usefulness of capecitabine. This comparison has several biases, and therefore the results should be considered with caution. Caution should also be applied when comparing our survival data with the lower survival rates reported by the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and the Asia-Pacific trials because of the different characteristics of the study populations. Results of the SHARP and Asia-Pacific trials were not available when our trial was designed. Those trials demonstrated a survival advantage for sorafenib, now considered standard treatment for advanced hepatocellular carcinoma HCC. However, the absolute advantage is still unsatisfactory (2.8 months among Western patients and 2.3 months among Asian patients) and is achieved at the expense of frequent toxicity. In fact, as many as 38% of patients discontinue treatment because of adverse events, and approximately 26% of patients require a dose reduction. In addition to the better disease control and survival rates, metronomic capecitabine also has a rather low toxicity profile. In fact, no treatment-related deaths were observed, and no patient withdrew from treatment because of adverse events. Most adverse effects were mild or moderate and were manageable with supportive care or a brief drug-free period. Although the toxicity rate among the first- and second-line cohorts seems similar, the efficacy was remarkably lower in the second-line setting. However, a median OS of approximately 10 months obtained in the second-line setting is an interesting result. In conclusion, metronomic capecitabine is safe and is associated with promising results in both treatment-naive and pretreated patients with advanced HCC who have preserved liver function.

Trial Information

Disease:	Hepatocellular carcinoma
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	None
Type of study - 1:	Phase II
Type of study - 2:	Single Arm
Primary Endpoint:	Progression Free Survival
Secondary Endpoint:	Overall Survival
Additional Details of Endpoints or Study Design:	

This was a single center, uncontrolled, phase II clinical trial including patients with advanced HCC defined by either vascular invasion or metastatic spread. All patients were either not candidates for or refractory to locoregional treatments. Based on these characteristics, patients belonging to Barcelona Clinic Liver Cancer (BCLC)-C and BCLC-B stage were enrolled. Histological confirmation of diagnosis was not mandatory, provided that American Association for the Study of Liver Diseases 2005 diagnostic criteria were fulfilled [1]. Other main inclusion criteria were: Eastern Cooperative Oncology Group performance status 0 or 1; Child-Pugh class A; life expectancy of at least three months; adequate hematological (hemoglobin ≥8.5g per deciliter; platelet ≥60 x 10^9 per liter; ANC 1.0 x 10^3/microliter), hepatic (total bilirubin ≤3.0 per deciliter; ALT/AST ≤5 x upper limit of normal [ULN]; INR ≤1.5) and renal functions (serum creatinine ≤1.2 x ULN). Any previous systemic treatment for HCC was also an exclusion criterion. Table 1 describes the characteristics of first-line patients. This requisite was amended after sorafenib had become available to allow inclusion of patients either

resistant to or intolerant of this drug, provided that they had been drug-free for at least 14 days at study entry. Primary objective was treatment efficacy, and progression-free survival (PFS) was chosen as primary outcome measure. The study was not designed on response rate because the investigators felt that antiangiogenic treatments, such as sorafenib [2] are more prone to induce RECIST-defined disease stabilization rather than objective response, so a conventional study design based on tumor response could result in a high probability to miss the endpoint. Secondary objectives were: objective response rate (ORR = complete + partial responses), evaluated per RECIST 1.0 criteria; overall survival (OS); and safety (type, incidence and severity of adverse events [AEs] reported). Tumor assessment was performed at baseline and, subsequently, every three months with multiphase spiral computed tomography (CT) scan or magnetic resonance imaging (MRI). Throughout the study, each lesion was followed-up with the same imaging technique employed at baseline. All the patients who received at least one dose of capecitabine and underwent restaging CT scan after three months or had progressed before were considered evaluable for efficacy (intention-to-treat analysis). Tolerability of this therapeutic schedule was known, thus a formal two-stages design was deemed unnecessary. As an additional safety measure, however, early study termination in case of observation of severe toxicity in more than five patients out of the first fifteen enrolled was scheduled. The primary endpoint of the study, PFS, is defined as the time elapsed from treatment initiation to disease progression or death. At the time of study design, although no systemic treatment with proven efficacy for HCC was available, doxorubicin was commonly used in clinical practice. Therefore, based on the phase III clinical trial by Gish and colleagues [3], a median PFS of 10 weeks for patients treated with doxorubicin was assumed as the result achievable with a systemic anticancer treatment, and an increase in median PFS $\geq$4 weeks was considered as clinically significant. For sample size calculation we assumed: (a) a one-sided alpha error of 0.05; (b) an accrual period of 27 months; (c) a follow-up period of 9 months; (d) the outcome (PFS) to be exponentially distributed. Under these assumptions, a sample size of 54 patients would ensure a power of at least 0.80 to detect an increase in median PFS of at least 4 weeks [4]. Considering a drop-out proportion of 10%, the trial was aimed at recruiting 60 patients. The trial also included an explorative study enrolling additional 30 patients in whom sorafenib treatment had failed (second-line cohort). This sample size was empirically determined. Table 2 summarizes the characteristic of second line patients. Patients' survival was estimated by Kaplan-Meier method and differences between subgroups compared with the log-rank test. A p-value of less than 0.05 was considered statistically significant in all analyses. To further investigate the impact of metronomic capecitabine on OS, an unscheduled comparison with an untreated population from the database of the Italian Liver Cancer (ITA.LI.CA) database, including 3027 HCC patients [5], was performed. Of these, 369 cases belonging to the BCLC intermediate or advanced stage [1] were initially considered for possible match with patients receiving metronomic capecitabine as first-line treatment. Further selection criteria were: treatment with palliative care, tamoxifen or other systemic drugs excluding sorafenib; Child-Pugh liver function class A; availability of complete clinical and tumour data. Eventually, 156 patients were available for matching. Match was possible for 50 patients, leading to a covariate distribution very similar between the two groups, especially as far as tumour characteristics is concerned (Table 3). **Treatment:** Patients received capecitabine 500 mg twice daily after meals, approximately every twelve hours. Drug administration was continuous, i.e. no drug-free periods were planned. Due to the low dose, no adjustments were allowed. In case of severe toxicity, defined as grade 3 or 4 by National Cancer Institute Common Toxicity Criteria for Adverse Events 3.0, a treatment interruption until improvement to grade 1 was required. If toxicity recurred at retreatment or failed to improve within two weeks, the patient was withdrawn from the study. Capecitabine administration was terminated in case of tumor progression at imaging, or worsening of hepatic function, defined as an increase of total bilirubin above 3 mg/dl or progression of liver failure to Child-Pugh score C. Concomitant treatment with sorivudine and other related agents, phenytoin, allopurinol, and coumarin-derived anticoagulants was not allowed during study. The use of medications and procedures potentially effective on HCC, including palliative radiotherapy were also not allowed. Prophylaxis of HBV reactivation with lamivudine or other antivirals was mandatory. The trial started in June 2008. After the first 15 patients had been evaluable for toxicity, four cases of grade 3 adverse events were observed. Therefore, enrollment continued until the planned sample size was achieved in December 2010. The data were considered ready for final analysis on September 15th, 2011.

Investigator's Analysis: Active and should be pursued further

Drug Information

Drug 1:	
Generic/Working name:	Capecitabine
Trade name:	Xeloda
Company name:	Roche
Drug type:	Other
Drug class:	Antimetabolite
Dose:	1000 milligrams (mg) per flat dose
Route:	oral (po)
Schedule of Administration:	500mg twice daily continously

Patient Characteristics

Number of patients, male:	73
Number of patients, female:	17
Stage:	advanced disease: first-line BCLC-B (26 pts) and BCLC-C (33 pts); second-line BCLC-B (15 pts) and BCLC-C (16 pts)
Age:	Median (range): 68 (44–88) first-line; 71(37–86) second-line
Number of prior systemic therapies:	Median (range): 0 (first.line); 1 (second-line)
Performance Status:	ECOG ● 0—27 (first-line); 13 (second-line) ● 1—32 (fisrt-line); 18 (second-line) ● 2—0 ● 3—0
Other:	This trial also included an explorative study which planned to enroll an additional 30 patients in whom sorafenib treatment had failed (second-line cohort). Finally, 31 patients received metronomic capecitabine as second-line systemic treatment after sorafenib failure. The complete characteristics of patients are reported in Table 2.
Cancer Types or Histologic Subtypes:	hepatocellular carcinoma: 90

Primary Assessment Method

Experimental Arm: Hepatocellular Carcinoma

Number of patients screened:	130
Number of patients enrolled:	90
Number of patients evaluable for toxicity:	90 (59 in first-line and 31 in second-line)
Number of patients evaluated for efficacy:	87 (58 in first-line and 29 in second-line)
Evaluation method:	RECIST 1.0
Response assessment CR:	3.44% first-line; 0% second-line%
Response assessment PR:	1.72% first-line; 0% second-line%
Response assessment SD:	51.7% first-line; 34.4% second-line%
Response assessment PD:	43.1% first-line; 65.5% second-line %
Response assessment other:	

(Median) duration assessments PFS:	first-line: 6.03; second-line: 3.27 months, CI: (first-line 3.43-8.37; second-line: 2.93-3.97)
(Median) duration assessments TTP:	na
(Median) duration assessments OS:	first-line: 14.47; second-line: 9.77 months, CI: (first-line: 10.53-17.13;second-line: 5.57-16.27)
(Median) duration assessments response duration:	
(Median) duration assessments duration of treatment:	
Experimental Arm: Total Patient Population:	
Number of patients screened:	
Number of patients enrolled:	
Number of patients evaluable for toxicity:	
Number of patients evaluated for efficacy:	
Evaluation method:	Other

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades

*No Change from Baseline/No Adverse Event

Assessment, Analysis, and Discussion

Completion:	Study completed
Pharmacokinetics / Pharmacodynamics:	Not Collected
Investigator's Assessment:	Active and should be pursued further

Discussion

In patients treated with first-line metronomic capecitabine, the median progression-free survival (PFS) was $>$6 months, much longer than the 2.5 months reported for historical control patients [3]. We believe that these results are successful. As expected for antiangiogenic treatments, the overall response rate was low, but the observation of two complete, long-lasting, responses with dimensional criteria such as RECIST is a further proof of the anticancer activity of metronomic capecitabine. In terms of both PFS and disease-control rate, our results are in line with those previously reported in a small group of HCC patients [6].

The overall survival (OS) observed (median of 14.5 months) is also encouraging and, interestingly, it was not different among BCLC-B and C patients. In segregated patients according to BCLC stage, median OS of the 26 BCLC-B patients was 14.47 months (95% C.I.: 10.47–18.47 months) and 15.50 months (95% C.I.: 8.66–22.34 months) for the 33 BCLC-C patients. Such a difference was not statistically significant ($p = 0.321$). This is understandable, considering that we enrolled BCLC-B patients not amenable to locoregional therapies, representing a subset with poorest prognosis among the heterogeneous group of patients with intermediatestage HCC. Additional evidence supporting the usefulness of capecitabine is provided by the finding that the median survival of treated patients almost doubled with respect to that of individually matched patients undergoing palliation. This comparison suffers from some biases and should be considered with caution. Caution should also be applied when comparing our survival data with the lower survival rates reported by the SHARP [7] and Asia-Pacific [8] trials, due to the different characteristics of the study populations. The use of sorafenib after capecitabine failure does not confer any benefit in terms of survival. Actually, 13 patients received sorafenib upon progression as second-line treatment, with no response, except a single one, and the median OS for 46

patients treated with capecitabine only was 15.9 months (95% CI: 8.77–23.09) while it was 12.2 months (95% CI: 11.01–13.46) for 13 patients treated with sorafenib in the second line ($p = 0.39$).

The efficacy of capecitabine as a second-line drug was lower. In fact, no ORR was observed, and PFS and OS were shorter than in the first-line cohort. Such a declining efficacy is, however, expected in a population with a poorer prognosis, and a median OS of about 10 months in these patients remains an interesting result, being similar to what was achieved, after failure of antiangiogenic treatment, by brivanib, a VEGFR/FGFR inhibitor [9].

When this study was designed, no effective treatment for advanced HCC was available. Nonetheless, doxorubicin chemotherapy was common practice and it was sometimes employed as control treatment in phase III clinical trials [3]. Tamoxifen [10], polychemotherapy [11], and nolatrexed [3] all failed to demonstrate any survival advantage over doxorubicin, and therefore only supportive care was recommended [1]. For this reason, we adopted doxorubicin as a benchmark for measuring the effect of capecitabine on PFS.

The SHARP [7] and the Asia-Pacific [8] trials dramatically changed this scenario. Sorafenib was associated with a statistically significant survival improvement, so that it is now considered as the standard treatment of advanced HCC patients with preserved liver function. However, the absolute advantage is unsatisfactory (2.8 months among Western patients; 2.3 months among Asians) and is achieved at the expense of frequent toxicity. In fact, up to 38% of patients discontinue treatment because of adverse events, and up to 26% require a dose reduction. HCC has a high angiogenic activity driven especially by VEGF [12]. The favorable effects of sorafenib on tumor vascularization and disease progressionare rapidly lost after treatment withdrawal, and a rebound in tumor growth can also be expected, which could be a class effect [13–16]. A brief course of treatment could also switch tumors to a more aggressive phenotype characterized by locally infiltrative growth and enhanced metastatic spread, as suggested by some studies [17–19]. Currently, no alternative drugs have been proven effective for HCC treatment, and many clinical trials to achieve this goal are in progress. Clinical research to identify more-effective and/or better-tolerated drugs is definitely warranted. Even conventional anticancer drugs exhibit an antiangiogenic effect, maximized by frequent and continuous administration, even daily. The target is switched from tumor cells to circulating endothelial cells and their precursors. This metronomic approach is characterized by good tolerability and can be conveniently put in practice with orally active drugs [20].

Capecitabine has been shown to have some clinical activity in advanced HCC [6, 21]. Theoretically, metronomic capecitabine could add to its antiangiogenic activity a direct antitumor effect.

Our results show that metronomic chemotherapy could be potentially interesting in the HCC setting. In fact, in addition to the results on patient survival, we confirmed the good toxicity profile of this approach even in a cirrhotic population: no treatment-related death was observed, and no patient withdrew from treatment due to AEs. Among them, nausea, diarrhea, hand-foot skin reaction, and mucositis can be considered drug-related, given capecitabine's toxicity profile [22]. However, they were mild or moderate in most cases, requiring only supportive care or brief drug-free periods. Instead, other AEs were probably related to the liver function decline rather than to capecitabine (Table 4 and 5). The incidence of AEs was not grossly different between first-line and second-line cohorts. Although the lack of difference could be due to the small sample size of the study, metronomic capecitabine is supposed to be well tolerated irrespective of previous sorafenib treatment.

Besides capecitabine, other orally active fluoropyrimidines administered with metronomic schedules have shown activity against HCC cells. Actually, metronomic uracil/tegafur (UFT) significantly postpones the onset of resistance to sorafenib [23], and metronomic S-1, alone or in combination with the targeted antiangiogenic drug vandetanib, prolongs survival without overt toxicities in mouse models of HCC [24]. A phase II trial of sorafenib plus metronomic UFT in Asian patients also showed that this combination is well tolerated and improves sorafenib efficacy [25].

In conclusion, metronomic capecitabine is a safe and likely active treatment in cirrhotic patients with preserved liver function and advanced HCC. The results of our study, as well as of previous seminal studies claim further investigations on this anticancer drug, alone or in combination with targeted antiangiogenic treatment.

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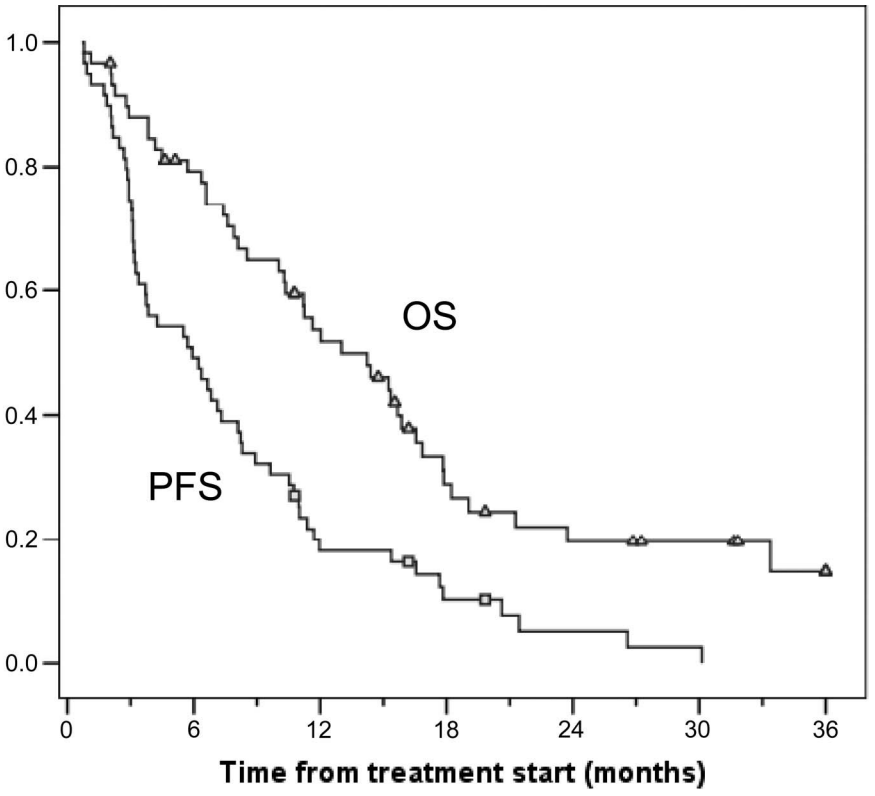
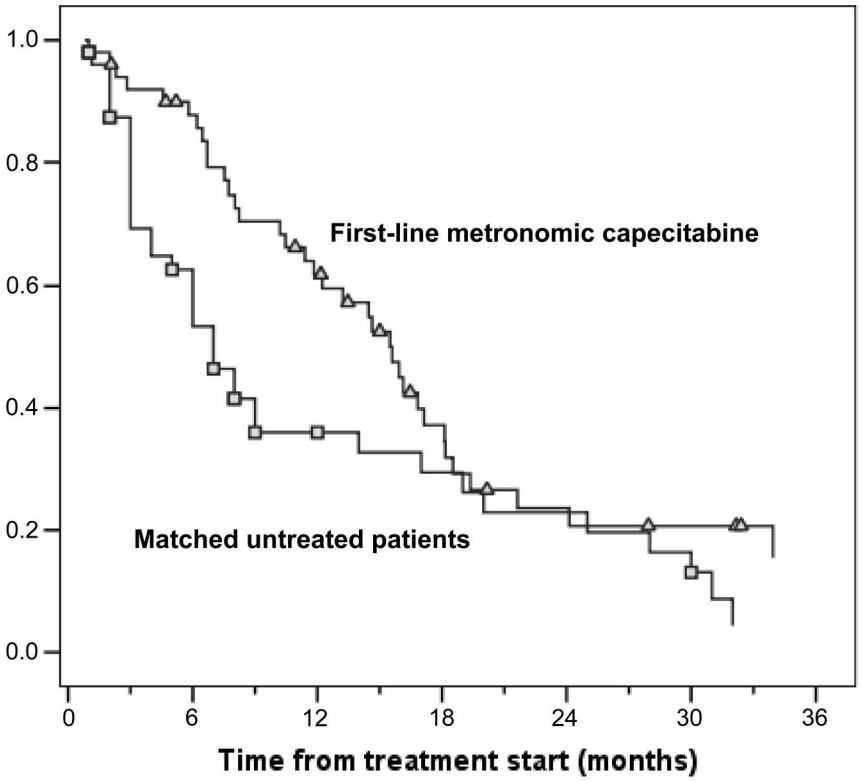
Figures and Tables



At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m
OS *n*	59	44	28	13	8	6	3
PFS *n*	59	29	10	5	2	1	0

Figure 1. Kaplan-Meier plot of PFS and OS for the first-line treatment cohort. The squares and triangles signify the censored patients in a group (squares) and in the other group (triangles) on the different curves.

Abbreviations: *n*, number of patients; OS, overall survival; PFS, progression-free survival.



At risk	0 m	6 m	12 m	18 m	24 m	30 m	36 m
Capecitabine *n*	50	41	28	14	8	6	3
Controls *n*	50	27	12	9	7	5	1

Figure 2. Kaplan-Meier plot of overall survival for 50 patients in the first-line treatment cohort and individually matched untreated patients from the Italian Liver Cancer (ITA.LI.CA) database. The squares and triangles signify the censored patients in a group (squares) and in the other group (triangles) on the different curves.

Abbreviation: *n*, number of patients.

Table 1. Characteristics of the 59 patients who received metronomic capecitabine as first-line treatment.

Characteristic	N	%
Age		
Median (Range)	67 (44–88)	
≤65	25	42
>65	34	58
Sex		
Male	48	81
Female	11	19
ECOG performance status		
0	27	46
1	32	54
Alpha-fetoprotein		
≤400 ng/ml	35	59
>400 ng/ml	24	41
Cirrhosis etiology		
HBV infection	9	15
HCV infection	40	68
Alcohol abuse	12	20
Other	3	5
Noncirrhotic liver	2	3
Number of HCC nodules		
≤5	30	51
6–10	12	20
>10	17	29
BCLC stage		
B	26	44
C	33	56
CLIP score		
0	4	7
1	19	32
2	26	44
3	8	14
4	2	3
Vascular invasion		
Absent	36	61
Present	23	39
Metastatic spread		
Absent	44	75
Present	15	25
Previous treatments		
None	17	29
Surgery	20	34
Locoregional treatments	37	63

Table 2. Characteristics of the 31 patients who received metronomic capecitabine after sorafenib failure.

Characteristic	N	%
Age		
Median (Range)	71 (37–86)	
≤65	9	29
>65	22	71
Sex		
Male	25	81
Female	6	19
ECOG performance status		
0	13	42
1	18	58
Alpha-fetoprotein		
≤400 ng/ml	18	58
>400 ng/ml	13	42
Cirrhosis etiology		
HBV infection	4	13
HCV infection	22	71
Alchohol abuse	4	13
Other	4	13
Noncirrhotic liver	1	3
Number of HCC nodules		
≤5	4	13
6–10	10	32
>10	17	55
BCLC stage		
B	15	48
C	16	52
CLIP score		
0	0	0
1	11	35
2	11	35
3	8	27
4	1	3
Vascular invasion		
Absent	20	65
Present	11	35
Metastatic spread		
Absent	20	65
Present	11	35
Previous treatments		
Surgery	11	35
Loco-regional treatments	24	77
Sorafenib	31	100
Sorafenib discontinuation reason		
Progressive disease	19	61
Intolerance	12	39

Table 3. Clinical covariates distribution for the 50 matched patients treated with metronomic capecitabine and their individual controls from the ITA.LI.CA database.

Variable	Capecitabine ($n = 50$)	No treatment ($n = 50$)	p
Median age (range)	67.5 (23–84)	67.0 (44–88)	0.259
Male sex	40 (80.0%)	35 (70.0%)	0.356
HBV infection	9 (18.0%)	11 (22.0%)	0.803
HCV infection	35 (70.0%)	34 (68.1%)	0.829
Alcohol abuse	11 (22.0%)	11 (22.0%)	>0.999
Diffuse HCC	17 (34.0%)	17 (34.0%)	>0.999
Presence of metastases	6 (12.0%)	6 (12.0%)	>0.999
Portal vein thrombosis	19 (38.0%)	19 (38.0%)	>0.999
BCLC Stage Advanced	25 (50.0%)	25 (50.0%)	>0.999
Median CLIP score (range)	2 (0–4)	2 (0–4)	0.708

Table 4. Recurrent adverse events observed among the 59 patients who received capecitabine as first-line treatment.

	All grades		Grade 3–4	
Event	**N**	**%**	**N**	**%**
Anemia	3	5.1	2	3.4
Ascites	4	6.8	3	5.1
Fatigue	14	23.7	2	3.4
AST/ALT elevation	3	5.1	1	1.7
Weight loss	3	5.1	0	0
Limb edema	7	11.9	1	1.7
Hepatic encephalopathy	3	5.1	1	1.7
Epigastric pain	7	11.9	1	1.7
Skin rash	4	6.7	0	0
Bilirubin elevation	6	10.2	5	8.5
Mucositis	4	6.8	0	0
Fainting	3	5.1	3	5.1
Hand-foot skin reaction	10	16.9	0	0
Thrombocytopenia	4	6.8	3	5.1

Table 5. Recurrent adverse events observed among the 31 patients who received capecitabine as second-line treatment.

	All grades		Grade 3–4	
Event	**N**	**%**	**N**	**%**
Diarrhea	2	6.5	0	0
Anemia	5	16.1	2	6.5
Fatigue	11	35.5	0	0
Pruritus	4	12.9	0	0
Hand-foot skin reaction	3	9.7	0	0
Weight loss	3	9.7	0	0
Deep vein thrombosis	2	6.5	2	6.5
Nausea	3	9.7	3	9.7
Epigastric pain	2	6.5	2	6.5
Bilirubin elevation	2	6.5	1	3.2
Ascites	3	9.7	3	9.7
Thrombocytopenia	2	6.5	1	3.2