Cancer Chemother Pharmacol (2012) 69:773–780
DOI 10.1007/s00280-011-1753-2

ORIGINAL ARTICLE

Phase II trial of sorafenib in combination with 5-fluorouracil infusion in advanced hepatocellular carcinoma

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Received: 16 August 2011 / Accepted: 20 September 2011 / Published online: 28 October 2011

Abstract *Purpose* Sorafenib improves overall survival and time to progression of advanced hepatocellular (aHCC) patients such as demonstrated in 2 phase III trials. However, aHCC patients' outcome is still poor despite these results. In order to improve the efficacy of systemic treatment for aHCC, we evaluated the combination of sorafenib plus 5-fluorouacil infusion in a phase II trial.
Methods Patients with aHCC not eligible for loco-regional therapies, Child-Pugh A-B, ECOG-PS 0-1, and without history of anti-cancer systemic treatment were enrolled. Treatment schedule was: sorafenib 400 mg/bid continuously and continuum infusion of 5-fluorouracil 200 mg/sqm/daily day 1–14 every 3 weeks.
Results Thirty-nine patients were enrolled: ECOG-PS 0-1: 29-10, Child-Pugh A-B: 36-3. Grade 3/4 (%) toxicities included: diarrhea 5.1/0, mucositis 20.5/2.6, hand foot skin reaction 20.5/0, skin rash 10.5/0, hypertension 10.3/0, hyperbilirubinemia 5.1/2.6, glutamic-oxaloacetic transaminase increase 10.3/0, glutamic-pyruvic transaminase increase 7.7/0, cardiac toxicity (one heart failure, two atrial fibrillation cases) 7.7/0, and bleeding (melena) in 2.6/0. One partial response was observed. Stable disease was obtained in 46.2% of patients with a median duration of 16.2 months. Median time to progression was 8 months (CI 95% = 5.7–10.4), and median overall survival was 13.7 months (CI 95% = 9.5–17.9).
Conclusions The results show an encouraging disease control rate, time to progression, and overall survival. The combination of sorafenib and 5-fluorouracil was feasible, and the side effects were manageable for patients carefully selected for liver function and performance status.

Keywords Hepatocellular carcinoma · Sorafenib · 5-Fluorouracil · Chemotherapy · Targeted therapy

Introduction

Hepatocellular carcinoma (HCC) represents 70–85% of liver cancers [11]. Worldwide, in 2007, 711,000 new cases and 680,000 related deaths were estimated [11, 27]. The prevalence is higher in developing countries especially in Asia and Africa but a stable increase was also observed in US and Europe [24]. Well-known risk factors for HCC are causes leading to cirrhosis such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol abuse and iron overload; therefore, HCC is the primary cause of death in cirrhotic patients [32].

According to Barcelona Clinic Liver Cancer (BCLC) staging classification, stage C patients present advanced tumors but conserved liver function and performance status (PS 0-2). They are no longer suitable for local therapy such as surgical resection, liver transplantation, percutaneus ablation or trans arterial chemoembolization. Untreated

ClinicalTrials.gov ID: NCT00619541.

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stage C patients have a poor prognosis with a median overall survival (OS) of 6 months [23]. These patients are candidates for systemic therapies and, to date, sorafenib is the only drug able to improve OS in randomized phase III trials [6, 25].

Sorafenib is a multi-target inhibitor acting mainly on kinase activity of BRAF, vascular endothelial growth factor receptors (VEGFRs 1, 2, and 3), and platelet-derived growth factor receptor β (PDGFRβ) [5, 33]. Sorafenib exerts anti-tumor activity in HCC cell lines and xenograft models [22], through inhibition of angiogenesis, decrease in cell proliferation and induction of apoptosis [5, 34].

Standard chemotherapy, in mono or combination schedules, has been largely tested in HCC patients with response rate ranging from 0 to 28%, but the majority of phase III studies failed to demonstrate an OS improvement [26]. Doxorubicin, 5-fluorouracil (5-FU), and cisplatin demonstrate a limited anti-cancer activity in HCC [16, 26], and 5-FU is frequently used for the treatment of gastrointestinal cancers [16, 26] and presents cytotoxic activity against HCC cell lines and xenograft. In HCC patients, phase II trials report response rate up to 28% and a favorable toxicity profile for 5-FU treatment [1, 7, 8, 18, 21].

Despite the interesting results of sorafenib in advanced HCC patients, treatment outcome is still poor and necessitates improvements. To address this issue, we evaluated the combination of sorafenib plus 5-FU infusion in a phase II trial. A phase I trial previously confirmed the treatment feasibility for sorafenib and 5-FU combination [10].

Patients and methods

This is a mono-center non-randomized phase II trial performed in advanced HCC patients. The trial was approved by the ethics investigation committee of Pisa University Hospital, conducted in accordance with Declaration of Helsinki and registered on clinicaltrial.gov (NCT00619541). Informed consent was obtained from each patient.

Patients' eligibility

Patients were eligible if they had measurable disease, proven diagnosis by histology or cytology, inoperable HCC and if they had not received prior systemic anti-cancer treatment. Inclusion criteria were Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0 or 1; Child-Pugh score A or B; life expectancy longer than 12 weeks and adequate hematologic, hepatic, and renal function. Status of HBV and HCV infection was collected at baseline from medical history and laboratory tests. Exclusion criteria were fibrolamellar variant, brain metastasis, pregnancy or lactation, presence of congestive heart failure defined as New York Heart Association (NYHA) class III or IV, serious cardiac arrhythmias, active coronary artery disease or ischemia. Patients who experienced previous malignancies within 3 years or patients who presented clinically significant gastrointestinal bleeding within 1 month from the enrollment were not eligible.

Treatment and dose modifications

Patients received sorafenib 400 mg twice a day and infusion of 5-FU 200 mg/m^2/daily from day 1 to day 14 every 21 days. After 1 year of treatment, without evidence of tumor progression, only sorafenib administration was continued. Treatment was continued until disease progression (PD) or unacceptable toxicity. Dose reductions or delays were scheduled for drug-related toxicities. Toxicities were graded according to National Cancer Institute (Bethesda, MD) Common Toxicity Criteria v3.0. For grade 3–4 adverse events, patients received dose reduced to 1 level lower (Table 1) and the treatment was delayed until toxicity improved to grade 2 or better, or discontinued if the recovery time was longer than 3 weeks. Patients, who experienced drug-related grade 4 non-hematologic toxicities, were treated at two dose levels lower at the first appearance and withdrawn at the second. The evaluation scale used for hand–foot skin reaction (HFS) has been previously reported [3]. Blood pressure was measured by sphygmomanometer twice a week and at the revaluation visits.

Response assessment

Tumors were measured by computer tomography according to RECIST criteria [30] at baseline and every 9 weeks thereafter (3 cycles). Responses were scored as complete response (CR) or partial response (PR) only if confirmed after 4 weeks. Stable disease (SD) was confirmed if stabilization lasted 18 weeks or longer.

Statistical analysis

Response rate underestimates the effect of sorafenib on patients' survival; consequently, we selected Disease

Table 1 Sorafenib and 5-FU dose levels

Drug	Dose level	Dose	
Sorafenib	Level 1	400 mg × 2	Daily
	Level 2	200 mg × 2	Daily
	Level 3	200 mg × 1	Daily
5-Fluorouracil	Level 1	200 mg/m^2/daily	Day 1 → 14 q21
	Level 2	150 mg/m^2/daily	Day 1 → 14 q21
	Level 3	100 mg/m^2/daily	Day 1 → 14 q21

Control Rate (DCR: number of non-progressive disease after 18 weeks of treatment) as the primary endpoint. Similar considerations have been reported for the selection of primary endpoint of trials evaluating imatinib in gastrointestinal stromal tumors [15, 29]. Secondary endpoints were OS, time to progression (TTP), progression-free survival (PFS), response rate (RR), duration of response, duration of stable disease, and toxicity profile.

Simon's optimal two-stage design for phase II clinical trials was applied to calculate the sample size that minimizes the number of patients accrued. The sample size was calculated on the assumption of α error = 0.05, β error = 0.20. The null hypothesis (P0) and the alternative hypothesis (P1) were set at DRS 40 and 60%, respectively. The reported DCR for sorafenib mono-therapy was 43% [25]. The minimal requirement was 7 no-PDs out of 16 treated patients for the first step and 23 out of 46 to complete the study.

TTP was calculated from the first day of treatment until documented disease progression; patients who did not experience disease progression were censored. PFS was calculated from the first day of treatment until documented disease progression or death by any cause; living patients without any evidence of tumor progression were censored. OS was assessed from the first day of treatment until death date; living patients were censored. Response duration was calculated from the first evidence of response to PD; patients who did not experience disease progression were censored. SD duration was assessed from the date of first evaluation until PD; patients who did not experience disease progression were censored.

Results

Demographics

From October 2006 to November 2008, 39 patients had been enrolled in the study. The study was discontinued for a relevant slowdown in patient's enrollment in the last 4 months. Patient's median age was 67 years (range: 41–83). Twenty-five (64%) patients were BCLC stage C and 14 (26%) stage B not anymore suitable for local therapies. Patient's characteristics are summarized in Table 2. Thirty-eight patients were evaluable for survival, because one was lost at follow-up. The first revaluation (after 9 weeks) was assessable in 33 patients and the second in 30 (after 18 weeks).

Dose and duration of therapy

Median treatment duration was 4.6 months (95% Confidence Interval (CI): 2.1–7.5), median number of treatment cycles was 7 (range: 1 to 37), one patient was still in treatment after 37 cycles, and 51.2% of patients (20/39) received more than six cycles. Five patients discontinued the treatment after one cycle for toxicity and one patient after 2 cycles for PS impairment. The reasons for treatment

Table 2 Patients characteristics

	Percentage	Number of patients
Sex		
Male	85	33
Female	15	6
Principal risk factors for HCC		
HBV	26	10
HCV	59	23
HDV	5	2
HBV + HCV	8	3
Alcohol	5	2
None	18	7
ECOG-PS		
0	74	29
1	26	10
2	0	0
Child-Pugh		
A	92	36
B	8	3
TNM Stage UICC 6th [17]		
I	0	0
II	28	11
IIIA	28	11
IIIB	3	1
IIIC	20	8
IV	18	7
Ne	3	1
Extrahepatic disease		
Present	41	16
Absent	59	23
Macroscopic vascular invasion		
Present	18	7
Absent	82	32
BCLC stage		
B	24	14
C	64	25
Previous treatments for HCC		
Surgical resection	13	5
PEI	18	7
RF	10	4
Thermo-ablation	8	3
TACE	54	21

Ne not evaluable, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HDV* hepatitis D virus, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *UICC* Union for Internal Cancer Control, *BCLC* Barcellona liver cancer classification, *HCC* hepato cellular carcinoma, *PEI* percutaneous ethanol injection, *TACE* trans arterial chemoembolization

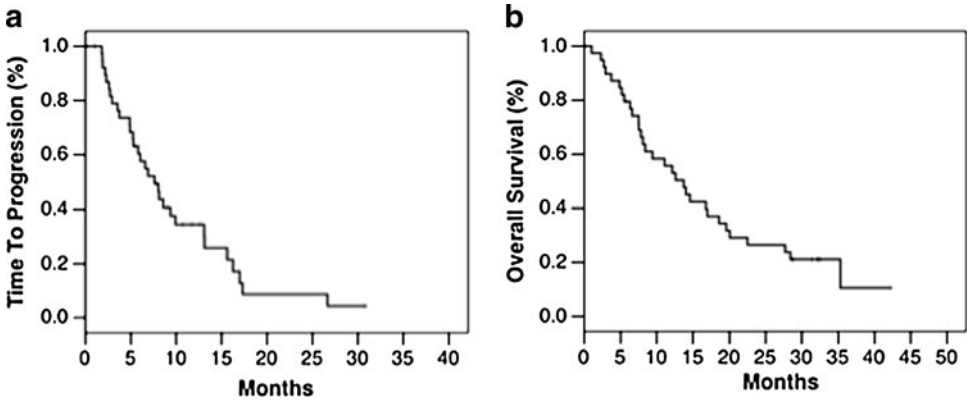

Fig. 1 Time to progression (**a**) and overall survival (**b**) of advanced HCC patients treated by sorafenib 5-fluorouracil combination

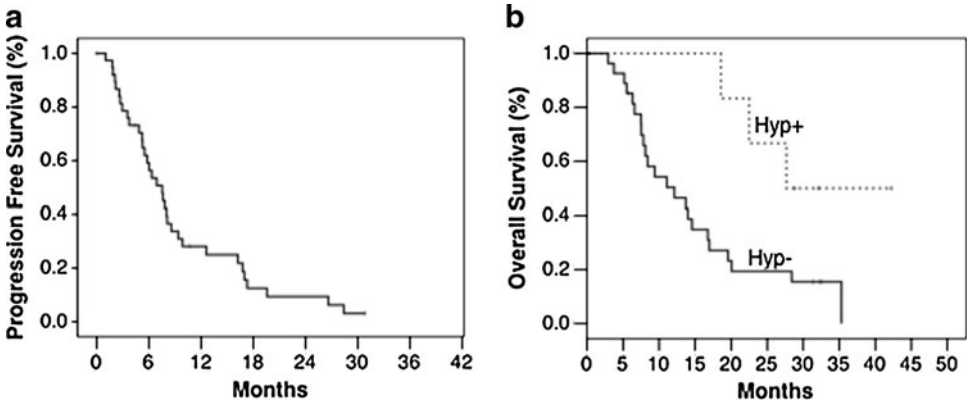

Fig. 2 Progression-free survival (**a**) of advanced HCC patients treated by sorafenib 5-fluorouracil combination. **b** Overall survival of patients treated by 3 or more cycles of sorafenib 5-fluorouracil who experienced (Hyp+) or not (Hyp−) hypertension

discontinuation were progression for 16 patients, toxicity for 11, impairment of liver function for 7, and patient decision for the remaining 4. Twenty-five patients received delayed treatment, and 23 patients necessitated dose reduction due to treatment toxicity.

Efficacy

DCR was 48.7%. After 6 cycles of treatment, 19 patients did not experience disease progression out of 30 evaluable. One patient obtained a PR (2.6%), 18 a SD (46.2%), 11 progressed (28.2%), and the remaining 9 were not assessable for response. The patient who reached PR response did not show radiologic evidence of progression and treatment was discontinued for impairment of liver function. The radiologic follow-up demonstrated a PR duration longer than 12.5 months. The median SD duration was 16.2 months (95% CI: 5.3–27.1 months). The median TTP was 8 months (95% CI: 5.7–10.4; Fig. 1a), the median PFS was 7.5 months (95% CI: 5.4–9.6; Fig. 2b), and the median OS was 13.7 months (95% CI: 9.5–17.9; Fig. 1b).

Toxicity

The most common drug-related adverse events were HFS, diarrhea, and mucositis (Table 3). Other grade 3–4 toxicities were dermatological rashes (10.3%), hypertension (10.3%), liver toxicity (hyperbilirubinemia 7.7%, glutamic-oxaloacetic transaminase (GOT) increase 10.3% and glutamic-pyruvic transaminase (GPT) increase 7.7%), cardiac toxicity (2 cases of atrial fibrillation and 1 case of heart failure), and one case of gastrointestinal bleeding. Treatment-related hypertension was more frequent in patients with history of hypertension (50%; 5 patients) than in patients without (10%; three patients; Fisher's exact test $P = 0.016$, Table 4). Sixty-day mortality rate was 3%; the only death within the first 60 days from starting therapy was possibly related to treatment and due to liver failure.

Subgroup analysis

For BCLC stage B and C, OS was 16.8 months (95% CI: 3.2–30.3) and 12.1 (5.1–19.1; $P = 0.288$), TTP was 7.6 (1.3–13.9) and 8.6 (5.7–11.4; $P = 0.889$), and PFS was 8.1 (95% CI: 4.3–11.9) and 6.9 (95% CI: 4.5–9.3), respectively.

Thirty-two percent of patients who reached PR or SD (6/19) experienced treatment-related hypertension, whereas none of the patients who progressed had this side effect (Fisher's exact test $P = 0.046$). Patients who experienced hypertension showed a better OS (LogRank $P = 0.008$), even in the group of patients who received 3 or more treatment cycles (hypertension group median OS 27.7 months; 95% CI not evaluable because only 1 event

Table 3 Toxicity: max toxicity grade for each patient observed

	G1#	G1%	G2#	G2%	G3#	G3%	G4#	G4%
Nausea	11	28.2	2	5.1	0	0.0	0	0.0
Vomiting	5	12.8	0	0.0	0	0.0	0	0.0
Diarrhea	14	35.9	7	17.9	2	5.1	0	0.0
Mucositis	6	15.4	3	7.7	8	20.5	1	2.6
HF syndrome	8	20.5	6	15.4	8	20.5		
Skin rash face	2	5.1	0	0.0	1	2.6	0	0.0
Skin rash truncus	2	5.1	1	2.6	2	5.1	0	0.0
Skin rash extremities	0	0.0	1	2.6	1	2.6	0	0.0
Fatigue	7	17.9	5	12.8	0	0.0	0	0.0
Hypertension	3	7.7	1	2.6	4	10.3	0	0
Fever	5	12.8	1	2.6	0	0.0	0	0.0
Anorexia	0	0.0	1	2.6	0	0.0	0	0.0
Hyperbilirubinemia	1	2.6	4	10.3	2	5.1	1	2.6
GOT	3	7.7	2	5.1	4	10.3	0	0.0
GPT	3	7.7	2	5.1	3	7.7	0	0.0
Bleeding	2	5.1	0	0.0	1	2.6	0	0
Cardiological*	0	0.0	0	0.0	3	7.7	0	0.0

HF syndrome hand–foot syndrome, *GOT* glutamic-oxaloacetic transaminase, *GPT* glutamic-pyruvic transaminase

* Two cases of atrial fibrillation and one case of heart failure

available; no-hypertension group median OS 12.1; 95% CI: 5.6–18.7 months; Log Rank $P = 0.02$; Fig. 2b, Table 4).

Discussion

The combination of sorafenib and 5-FU infusion resulted in an encouraging OS and TTP in advanced HCC patients with a median of 13.7 and 8 months, respectively. The schedule was feasible for the treatment-related toxicity; however, an intensive follow-up of liver function and a careful selection of the patients are recommended.

The OS is equal to what was reported for the doxorubicin/sorafenib combination [2] and comparable to the combination of sorafenib plus octreotide: 12 months [28]. Sorafenib combination schedules present an increased OS compared to single-agent (9.2 [3]–10.7 months [25]) suggesting the possibility to improve treatment efficacy with an appropriate association strategy. However, the comparison between different trials is difficult to interpret, especially for HCC, because several factors influence the patients' outcome including Child-Pugh score, performance status, presence of extra-hepatic disease and macroscopic venous invasion. In this scenario, minimal variations among inclusion criteria select patients' groups with different prognosis. In our series, the presence of BCLC stage B patients (26%) could significantly impact the survival data; however, median OS (12.1 months) and TTP (8.6) observed for stage C patients are still encouraging compared to previous reports.

Based on these considerations, a randomized design should be chosen, at this time, for a phase II trial in HCC patients; different from what was reputed when the trial was designed. However, inclusion criteria were similar to those chosen by Abou Alfa et al. [3], and patients were enrolled from the same population of sorafenib single-agent trials [3, 25] in which we largely participated.

Survival parameters of sorafenib trials in the Asian population are not comparable with ours because a more severe prognosis is usually described in Asian patients (median overall survival 6.5 [6]–4.8 [12] months) even if sorafenib is able to improve patients' outcome in this setting [6].

PR was observed in only one patient, although, the response rate is similar to those previously described and, usually, it is not predictive of prognosis for HCC patients. RECIST criteria seem to be inadequate for response evaluation of sorafenib treatment and modified criteria have been proposed [20] but still necessitate further validation. On these bases, we chose the DCR as primary objective of the study.

Combinations containing sorafenib and 5-FU or 5-FU prodrugs have been tested in HCC patients. Comparable DRS has been reported for the combination of sorafenib tegafur/uracil (58%) [13] and even a more promising results for sorafenib combination with capecitabine and oxaliplatin (DRS: 75%) [35] or with intra hepatic artery infusion of cisplatin and 5-FU (DRS: 88%) [31].

We observed a median TTP of 8 and a PFS of 7.5 months. The reported TTP is in line with the OS and comparable to the one obtained using doxorubicin/sorafenib combination (8.6 months) [2].

TTP considers censored those patients dead for causes other than PD, thus, TTP emphasizes the anti-cancer

Table 4 Characteristics of patients who develop treatment-related hypertension

	Treatment-related hypertension		
	No	Yes	*P* value
Sex			
Female	4	2	
Male	27	6	0.358
Age (range)			
Years	68 (41–83)	66 (57–78)	
Child-Pugh			
A	28	8	
B	3	0	0.492
ECOG-PS			
0	22	7	
1	9	1	0.323
Stage			
II	10	1	
IIIA	8	3	
IIIB	0	1	
IIIC	7	1	
IV	5	2	
Macroscopic vascular invasion			
No	25	7	
Yes	6	1	0.554
Extrahepatic disease			
No	19	4	
Yes	12	4	0.425
History of hypertension			
No	26	3	
Yes	5	5	0.016
History of thromboembolism			
No	30	8	
Yes	1	0	0.795
History of heart disease			
No	26	8	
Yes	5	0	0.295
Response			
PD	11	0	
SD	12	6	
PR	1	0	0.046*
Median treatment duration			
Months	3.8	7.4	
Median OS			
Months	9,4	27.7	0.008**
Median OS in patients who received ≥3 cycles			
Months	12.1	27.7	0.02**

ECOG-PS Eastern Cooperative Oncology Group Performance Status, *OS* overall survival, *PD* progressive disease, *SD* stable disease, *RP* partial response

P values were calculated using Fisher's exact test except for those labeled with ** that were calculated using Log Rank test for Kaplan–Meier curves.

* Fisher's exact test calculated PD versus SD + PR

treatment efficacy, whereas PFS incorporates several clinical aspects such as cirrhosis progression. These considerations could also explain the longer median TTP (8.6 months) associated with a shorter OS and PFS observed in stage C compared to B (7.6).

The observed toxicity is relevant but still comparable with adverse events previously described for single-agent treatment either with sorafenib or 5-FU [3, 6, 25], although, grade 3–4: HFS (20.5%), diarrhea (5.1%), hyper-GOT (10.3%), and hyper-GPT (7.7%) were more frequent.

The unstable liver function, caused by concomitant diseases, requires an intensive follow-up and frequent dose adjustments and treatment delay were necessary. Consequently, a high number of patients experienced dose reduction (23) and treatment postponement (25). Moreover, 11 patients discontinued the treatment due to toxicity-related adverse events and 7 patients for worsening of liver function. Compared to the favorable toxicity profile of sorafenib in mono-therapy for HCC patients, the combination feasibility was only slightly reduced by the overlapped adverse events of continued infusion of 5-FU and sorafenib.

Other combinations containing sorafenib and 5-FU or 5-FU prodrugs (capecitabine or tegafur/uracil) [4, 9, 13, 14, 19, 31], produce frequent G3-4 HFS (range 9–50%), diarrhea (2–9%), mucositis (3–4%), fatigue (3–15%), and hyper transaminases (13%). Conversely, our schedule more frequently produced G3-4 mucositis (23% vs. 3–4%). Schedules associating sorafenib with oral 5-FU prodrugs may facilitate patients' treatment compliance and maintain a favorable toxicity profile compared to 5-FU.

We observed a higher frequency of G3-G4 hypertension (10.3%) compared to previous reports [3, 25, 28], and, conversely, patients with a history of hypertension demonstrated an increased incidence of this event. In this series, patients who developed hypertension presented a longer median OS. Since the chance to experience hypertension may increase with treatment duration, we removed patients who received less than 3 cycles from this analysis. The higher frequency of treatment-related hypertension in patients who reached PR or SD compared to PD supports this hypothesis. However, this study was not designed for subgroup analysis and these observations need to be confirmed in a different series.

In conclusion, our data suggest that sorafenib–5-FU combination is feasible and introduces an interesting efficacy in advanced HCC patients. However, the main limitation of this trial was the necessity for a careful selection of patients that limited the accrual of patients, in a monocentric scenario, which lead to the discontinuation of the study when still incomplete. On the other side, the compromised liver function limits the possibility to treat these

patients. However, the promising results observed encourage further studies of possibly less toxic combinations. Several molecular pathways are now proven relevant for HCC tumorigenesis and mTOR, c-MET, IGF, and FGF, among others, are promising targets for treatment [32]. Combination schedules of drugs targeting these pathways could represent an efficient and well-tolerated systemic therapy.

Acknowledgments Bayer Pharma S.p.A, Milan, Italy founded this research. We thank Dr Clare Paterson and Donna Voeller who helped editing the paper.

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