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EXPERIENCE WITH EARLY SORAFENIB TREATMENT WITH mTOR INHIBITORS IN HEPATOCELLULAR CARCINOMA RECURRING AFTER LIVER TRANSPLANTATION

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Abbreviatons: AE, adverse events. AFP, alpha-fetoprotein. ALT, alanine transaminase. CI, confidence interval. CNi, calcineurin inhibitor. CT, computed tomography. CTCAE, Common Terminology Criteria for Adverse Events. DAA, Direct Antiviral Agent. GGT, gamma-glutamyltransferase. HCC, hepatocellular carcinoma. HCV, hepatitis C virus. HR, hazard ratio. IFN, Interferon. LT, liver transplantation. mTORi, mammalian target of rapamycin inhibitor. MC, Milan Criteria. MRI, magnetic resonance imaging. mTORi, mammalian target of rapamycin inhibitors. PET, positron emission tomography. RECIST, Response Evaluation Criteria in Solid Tumors. RFA, radiofrequency ablation. TACE, transarterial chemoembolization. US, ultrasound.

ABSTRACT

Background: Sorafenib (SOR) is currently used for hepatocellular carcinoma (HCC) recurring after liver transplantation (LT) when HCC is unsuitable for surgical/locoregional treatments. We evaluated safety and effectiveness of early introduction of SOR after HCC-recurrence. Methods: All patients with HCC-recurrence after LT treated with SOR in 2 centers were included (01/2008-06/2018). Baseline and on-treatment data were collected. Results: Fifty patients early treated with SOR for HCC-recurrence after LT (74% mammalian target of rapamycin inhibitor (mTORi), 54% HCC-treated at baseline) were enrolled. During 7.3 (0.3-88) months of SOR, all patients had at least one adverse event (AE), 56% graded 3-4. SOR was reduced in 68%, being AEs the main cause of reduction, and discontinued in 84% (60% symptomatic progression, 33% AE). Objective response was obtained in 16% and stable disease in 50%. Median time to radiological progression was 6 months (95% Confidence Interval [CI] 4-8). Thirty-three patients (69%) died, 94% for HCC progression. Median overall survival (OS) was 18 months (95%CI 8-27); 5-year OS was 18% (95%CI 4-32%). Baseline predictors of OS were SOR+mTORi (HR 0.4, 95%CI 0.2-0.9, p=0.04), previous curative treatments (HR 0.3, 95%CI 0.2-0.7, p=0.003) and alpha-fetoprotein>100ng/ml (HR 2.5, 95%CI 1.1-5.0, p=0.02). At multivariate analysis, HCC curative treatment was the only independent predictor (HR 0.4, 95%CI 0.2-1.0, p=0.04). Conclusions: Early and combined treatment with sorafenib and mTORi resulted in a favourable safety profile, while its effectiveness should be confirmed by meta-analysis of previous studies or by larger studies. Curative treatment for HCC resulted the only independent predictor of OS.

INTRODUCTION

Liver transplantation (LT) is an established treatment for hepatocellular carcinoma (HCC).[1] The risk of HCC recurrence varies between 8 to 20% depending on pretransplant-variables such as the tumor burden and the alpha-fetoprotein (AFP) level.[2-6] HCC recurrence clearly affects the expected survival, being as low as 3.3 months when only best supportive care was offered.[7] Management of HCC recurrence after LT is complex and challenging. In fact, the treatments are the same as those normally used in the pretransplant setting, although there is no evidence that such treatments could improve patient's survival in post-LT recurrence[8]; among these, systemic therapy with sorafenib (SOR) has been proposed. However, available data are limited to small experience of single centers and affected by great heterogeneity, particularly regarding the timing of SOR introduction and the association with immunosuppressive regimes[7-13]; in all these studies, however, SOR have been used only in advanced stages of recurrent HCC after LT, when surgical/locoregional treatments were unsuitable. Considering the metastatic nature of HCC recurrence, a systemic approach with SOR would be the most pragmatic treatment even in an early phase of the recurrence, eventually associated to surgery or locoregional treatments: to date there are no studies systematically addressing this approach.[14] Rate of SOR-related adverse events (AEs) varies greatly between studies, and the combination of SOR with certain immunosuppressive regimens appeared to be armful in some reports, while potentially useful in others, due to the anti-proliferative effects of some drugs like everolimus.[9,11,15,16] Particularly, one study reported grade 3-4 SOR-related AEs in 92% of patients and SOR discontinuation in 77%, while other studies reported an unexpected number of deaths related to gastrointestinal bleeding speculating a possible harmful interaction between everolimus and SOR.[9,11,15,16] On the other hand, the in vivo efficacy of everolimus was potentiated when combined with SOR in orthotropic models of human metastatic HCC, and this combination strongly inhibited the proliferation of HCC xenograft.[16,17]

To shed new lights on this topic, we retrospectively evaluated a cohort of liver transplanted patients treated with SOR as early as possible following HCC recurrence, with the aim to assess the safety and effectiveness of the early introduction of SOR in patients with HCC recurring post-LT.

PATIENTS AND METHODS

Study design, patients and endpoints

This is a retrospective evaluation of a cohort of prospectively enrolled patients in two different Liver Transplant Centers in Milan. The study is observational, investigator driven. All consecutive HCC transplanted patients, who developed cancer recurrence from January 2008 - when SOR became available in Italy - were included in this study whenever treated with SOR. The database was locked in October 2018. Baseline corresponded to first administration of SOR. A written informed consent was obtained from each patient according to the ethic committee and the ethical guidelines of the 1975 Declaration of Helsinki, as updated in 2004.

Patients transplanted for HCC were followed with thoraco-abdominal CT scan every 6 months for the first 5 years, and then annually. Serum AFP was measured every 3 months during the first year and every 6 months thereafter. In case of suspected HCC recurrence, biopsy was performed when the site of recurrence is reachable. Otherwise, the diagnosis was obtained by imaging associated with AFP levels increase. Once the diagnosis was obtained, SOR was started as soon as became available and its use safe (i.e. after healing of surgical wound in surgical patients). In patient already taking mammalian target of rapamycin inhibitor (mTORi)-based immunosuppression regimen (sirolimus or everolimus), mTORi was continued. In our centers, mTORi-based immunosuppressive treatments generally considered for all patients transplanted for HCC, on the basis of evidences that such an approach could increase the recurrence-free survival after LT for HCC:[18] dyslipidaemia, proteinuria above 0.5 g/die and logistical difficulties for a regular drug level dosage are eventually considered contraindications to mTORi. Systemic therapy was associated with surgery or locoregional treatment whenever judged appropriate, with a curative or palliative intent. For the analysis, treatments were considered with a curative intent if the removal of the neoplastic lesion led the patient HCC-free.

The following data were collected: demographics and pre-LT history, native liver histological tumor staging, immunosuppressive regimens, time, characteristics and treatments of HCC recurrence, AEs occurring during systemic treatment and/or immunosuppressive therapy. Performance status was evaluated according to the Eastern Cooperative Oncology Group (ECOG-PS).[19]

The primary endpoint was the safety of SOR treatment, evaluated by treatment related AEs, treatment duration and median daily dose administered. Secondary endpoint was effectiveness of SOR treatment, expressed as disease control rate, time to radiological progression and overall survival (OS) under SOR treatment.

Safety was assessed in all patients who received at least one dose of SOR, adverse events were graded according to v. 3.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose.[20] Hepatic function deterioration was also recorded.

Tumor response was assessed every 2 months during treatment and follow-up using CT-scan or MRI, according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[21] Time to radiological progression was defined as the time elapsed from baseline to disease progression according to modified RECIST criteria for HCC. First radiological progression was classified according to Reig et al. (i.e. ≥20% increase in tumor size against a known baseline lesion - intrahepatic growth or extrahepatic growth; new intrahepatic lesion, or new extrahepatic lesion and/or vascular invasion).[22] Overall survival was measured from the date of starting SOR until the date of death from any cause or date of the last visit. Baseline variables were also analysed in order to identify predictors of OS.

Treatment schedule, dose modification and interruption

Sorafenib (Nexavar; Bayer, Basel, Switzerland) was administered at a dose of 400 mg twice daily following the indications provided by the manufacturer.[23] Contraindications to SOR were: unstable coronary artery disease or recent myocardial infarction, severe arterial hypertension not responsive to pharmacological therapy, prolongation of QTc interval, hypersensitivity to the active substance or

to any of the excipients. If patients were eligible to surgery, SOR was started after healing of surgical wound.[23,24]

All grade 3/4 AEs or clinically relevant grade-2 toxicity resulted in dose modification or treatment interruption whenever the AE was clinically relevant. A dose reduction (400 mg once daily) or temporary interruption was maintained until the symptoms resolved to grade 1 or 2 according to the guidelines provided by the manufacturer, followed by a re-escalation to the full-dose.[23,24] Dose was also modified in patients showing grade-2 toxicity on patient's request or whenever a grade 2 AE was judged clinically relevant. Hepatic deterioration was another criterion for dose modification or interruption. Treatment was continued until symptomatic progression, unacceptable adverse events, patient's willingness or death.

The immunosuppression regimens were modified, as recurrence occurred, according to the policy of each center, to reduce immunosuppressive effects.[18] The mTORi could have been administered in monotherapy or in association with CNi, with an expected target level of 4–10 ng/mL for mTORi, 3-5 ng/mL for tacrolimus and around 100 ng/mL for cyclosporine.

Statistical Analysis

We used standard statistics (median and range for continuous variables, percentage for categorical variables) to describe baseline series characteristics and safety data, and nonparametric tests (Mann-Whitney test for continuous variables, Pearson's Chi-Square/Fisher exact test for categorical variables) to compare characteristics distribution. Survival time was computed as the interval between first administration of SOR and death (survival after SOR). Survival time was censored at the date of last contact in living patients. Survival curves were estimated with the nonparametric Kaplan-Meier method. Cox proportional hazards model was used to investigate the association between OS and baseline variables. In particular, baseline predictors of OS at the univariate and multivariate analysis were analysed by calculating the hazard ratio of death. Calculations were done using SPSS Statistics Program.

RESULTS

Fifty patients were enrolled. Patients' baseline characteristics are shown in Table 1. HCC recurred after a median of 16 months (2-118) since LT. SOR was started after a median of 2.7 months (0.1-8.2) following HCC recurrence. At SOR start, 37 patients (74%) were on therapy with mTORi, which was everolimus in all cases. An HCC treatment with curative intent was performed in 27 (54%) patients 2.7 months (0.3-109) from SOR start: among these, 25 (95%) patients underwent surgery; one patient was treated by RFA of a single HCC hepatic nodule and 1 patient cryo-ablation of a heart mass.

Safety analysis

Sorafenib was administered for a median of 7.3 months (0.3-88) in the overall group and for 12 months (0.3-76) in the subgroup of patients taking also mTORi. All patients had at least one SOR-associated AE: 22 (44%) graded 1–2; 28 (56%) grade 3-4. No significant increase of SOR-related AEs occurred in patients treated with SOR+mTORi based regimen compared to patients treated with SOR+other immunosuppressive regimens, except for any grade of hand-foot skin reaction (HFSR; the difference was lost considering grade 3-4 HFSR, see Table 2). Among all the baseline variables, no predictors of AE were identified. SOR dose was reduced in 34 patients (68%) and the median daily dose of SOR was 400 mg. AE was the main cause of dose reduction (n=31, 91%), followed by liver graft dysfunction (n=3, 9%). SOR was permanently discontinued in 42 patients (84%): symptomatic progression of HCC in 25 (59%), AE in 14 (33%), liver graft dysfunction in 2 (5%), HCC complete remission in 1 (2%). Two patients treated with SOR+mTORi died: one due to massive gastrointestinal bleeding from a severe hemorrhagic gastropathy without any signs of portal hypertension, the other due to severe diarrhea 4 months after starting SOR, that persisted despite interruption of SOR and everolimus.

The main mTORi-related AEs were nephrotic range proteinuria (n=3, 8%), which resolves after discontinuation of treatment without deterioration of renal function; oral ulcers (n=5, 13%); hypertriglyceridemia (n=7, 17%); ankle oedema (n=5, 13%). Dosage of mTORi was reduced in 12 (32%) patients and drug-discontinuation in 10 (27%) due to AEs occurrence.

Two patients treated with SOR+mTORi developed a severe alteration of liver blood tests after 2 and 4 months of treatment. Liver biopsy showed early chronic rejection according to Banff Working group criteria. These patients were treated with steroids plus higher doses of immunosuppressive therapy. In one of these patients a second liver biopsy was performed 1-year later due to persistently biochemical alteration and histological signs of drug injury were found: everolimus was discontinued with a significant improvement in blood tests. Seven patients suffered a mild increase in liver enzymes that quickly improved after immunosuppression therapy increase.

Effectiveness and Survival

The median follow-up after SOR initiation was 14 months (1.5-103). Overall, disease control rate was obtained in 33 (66%) patients: objective response in 8 (16%) and stable disease in 25 (50%). First radiological progression during the treatment occurred in 33 patients (66%) with a median time to progression of 6 months (95%CI 4-8; Figure 1): the pattern of progression was new extra-hepatic lesions in 6 (18%), increase of preexistent extra-hepatic lesions in 12 (36%), new intra-hepatic lesion in 5 (15%) and both increase in number and size of the lesions in 10 (30%), respectively. Among patients with disease progression during SOR, a locoregional treatment with palliative intent was performed in 14 (42%) patients to reduce tumor extension or to relief tumor-symptoms: 5 were treated by TACE, 6 by bone radio-therapy, 2 by decompressive laminectomy and 1 by endobronchial approach for bronchial obstruction.

Thirty-three (66%) patients died: 31 for HCC progression, 1 patient for severe diarrhea and 1 for gastrointestinal bleeding. The 1- and 5-year cumulative probability of OS from SOR start were 65% (95%CI 50-78%) and 18% (95%CI 4-32%), respectively, with a median OS of 18 months (95% CI 8-27) (Figure 2). At univariate analysis, baseline variables associated with an increase in OS were:

treatment with SOR+mTORi (HR 0.4, 95%CI 0.2-0.9, p=0.04, Figure 3), HCC treatment with curative intent (HR 0.3, 95%CI 0.2-0.7, p=0.003), AFP levels > 100 ng/mL (HR 2.5, 95%CI 1.1-5.0, p=0.02). By univariate analysis, histological "Milan-in" and "Milan-out" groups (homogeneous for baseline clinical variables) showed no statistical difference in OS.

Further analyses were conducted dissecting the ancillary role of mTORi: the OS was significantly longer in 27 patients treated with CNi+mTORi than in 13 patients treated with CNi alone (HR 0.32, 95%CI 0.13-0.78, p=0.013). By univariate analysis, no statistical difference was found according to immunosuppressive regimen [i.e. a) mTORi alone (10 pts) vs CNi without mTORi (13 pts), p=0.772 - removing from the expected anti-tumorigenic effect of mTORi a possible confounding factor of a pro-tumorigenic effect of CNi; b) mTORi alone vs others, p=0.280].

At multivariate analysis, only HCC curative treatment before SOR maintained a statistical significance (HR 0.4, 95%CI 0.2-1.0, p=0.04) (Table 3): the cumulative probability of OS from SOR start according to curative treatment was 81% (95%CI 66-96) in curative group versus 46% (95%CI 25-67) in the other one at 1-year, confirming its positive impact on survival (p=0.003) (Figure 4). No significant difference in TTP was found according to combination of SOR+mTORi vs SOR alone (p=0.40). The median OS from HCC recurrence was 28.8 (95%CI 18.9-38.7).

DISCUSSION

The study assessed for the first time the safety and effectiveness of early introduction of SOR in patients with HCC recurrence post-LT. In fact, at variance from previous studies, SOR was administered as early as possible after HCC recurrence, a strategy that extended treatment duration in the context of a favourable safety profile even when SOR was combined with mTORi.

We believe that an early introduction of SOR after HCC recurrence led us to treat asymptomatic patients in good clinical conditions, the best candidates in terms of treatment tolerance and survival. Other factors that may have enhanced the drugs tolerability was the absence of cirrhosis together with the absence of viruses' replication in those patients with an history of HBV and HCV infection (67% HCV-RNA negative).

In our study we treated patients until symptomatic progression of the tumor, being most of them SOR-tolerant patients after dose-modification according to AE. For this reason, treatment duration and OS frequently overlapped in our patients and led to an unexpected prolonged time to first tumor progression, even longer than generally observed.[7-14,24-30] An additional explanation is the reduction of tumor burden in our case series by surgery or loco-regional treatments, with a gain in terms of survival as shown by multivariate analysis.

Some concerns emerged on an increase of severe AEs due to the association of SOR and mTORi, with four cases of drugs-related deaths among 197 treated patients, following haemorrhage.[31] In our study, the co-administration of SOR and mTORi did not result in an increase of drug-related AEs, neither in terms of frequency nor in terms of severity, compared to the group of patients treated with SOR alone. Only HFSR emerged more frequently in the former group, however without an increased number of grade 3/4 AEs leading to dose reduction or discontinuation. The only two severe AE occurred at the beginning of our experience in the management of the combination treatment and were already published by one of the two group involved in this analysis.[32] Moreover, the concomitant administration of mTORi and SOR did not result in unexpected fluctuations of everolimus serum levels. Thanks to the initial experiences, the close clinical and biochemical monitoring we performed thereafter, probably led to a prompt tuning of both drugs to avoid either unacceptable AE or severe dysfunction of the graft, increasing the compliance and therefore treatment duration. As a result, premature and permanent discontinuation of treatment was uncommon in our study, which reported median treatment duration of 8 months.

The prolonged treatment duration paralleled with the excellent survival date observed in the whole cohort, longer than previously shown with a delayed introduction of SOR.[7-13,33] Thanks to the presence of a small group of patients treated with SOR only with similar baseline characteristics compared to the group of patients treated with SOR+mTORi, we could observe a gain in terms of median OS of 12 months (p=0.03) for the latter group, even when we considered separately those patients treated with mTORi±CNi. The only independent predictor of survival, however, was the

previous curative treatment of recurrence by surgery or loco-regional treatments, suggesting an action of consolidation of SOR of the result obtained.

Our study has some limitations: the retrospective design, the lack of a control arm treated with a late SOR approach and the limited number of patients treated with SOR only that does not allow a direct comparison with the combination with mTORi. However, the study has several strengths: this is the largest consecutive series of patients treated with SOR in the post transplant and the first addressing the early treatment with SOR in this setting. Moreover, despite the retrospective design of the study, the cohort is homogeneous regarding the baseline features and the patient management.

In conclusion, we demonstrated that the early start of SOR in HCC recurrence post-LT has a good safety profile when a prompt tuning of drug dose was applied and led to an unprecedented overall survival. Curative treatment for HCC resulted the only independent predictor of OS, while a possible role of the association SOR+mTORi should be confirmed by either meta-analysis of previous studies or by larger multicenter studies, in the waiting for new second line drugs that will become available in the near future also in this clinical setting.[34-36]

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FIGURE LEGEND

Figure 1 - Cumulative probability of HCC progression.

Figure 2 - 5-year cumulative patients' survival in the overall population.

Figure 3 - 5-year cumulative patients' survival according to the combination of SOR with mTORi.

Figure 4 - Cumulative patients' survival according to the curative treatment of HCC.

Table 1. Baseline clinical and demography features of 50 patients enrolled in the study.

Features	**Overall (n=50)**
Age, years*	57 (41-75)
Male, N.	40 (80%)
Cirrhosis, N.	0
Bilirubin, mg/dL*	0.65 (0.30-1.88)
Albumin, g/dL*	4.40 (3.17-4.80)
Performance status 0, N.	50 (100%)
Liver disease etiology, N.	
HCV§	31 (62%)
HBV	12 (24%)
Others	7 (14%)
Native liver histology, N.	
Milan-in	22 (44%)
Microvascular invasion	25 (50%)
Edmonson grade 3 or 4	29 (58%)
HCC recurrence time, months*	16 (2-118)
Time from HCC recurrence to SOR treatment, months*	2.7 (0.3-109)
HCC recurrence pattern, N.	
Liver only	5 (10%)
Intra and extra-hepatic	18 (36%)
Extra-hepatic only	27 (54%)
AFP levels, median, ng/mL*	8 (1-48000)
AFP levels > 100 ng/mL, N.	26 (52%)
HCC-curative treatment, N.	27 (54%)

Immunosoppressive regimen	
CNi+mTORi	27 (54%)
mTORi	10 (20%)
CNi	6 (12%)
CNi+MMF	7 (14%)

*Median (range); Hepatitis B virus (HBV); Hepatitis C virus (HCV); Hepatocellular carcinoma (HCC); Alpha-fetoprotein (AFP); calcineurine inhibitor (CNi), cyclosporine or tacrolimus; Mammalian Target of Rapamycin inhibitor (mTORi), everolimus or sirolimus; mycophenolate mofetil (MMF); §HCV-RNA positive 4/31.

Table 2. Sorafenib-attributable adverse events in patients with hepatocellular carcinoma recurring after liver transplantation

	Overall (n=50)			SOR+mTORi (n=37)		SOR (n=13)		p-value§ (SOR+mTORi vs SOR)	
Adverse Events*	**Any Grade**	**Grade 3-4***	**Time to any grade AE (days) ****	**Any Grade**	**Grade 3-4***	**Any Grade**	**Grade 3-4***	**Any Grade**	**Grade 3-4***
Any type, N.	50 (100%)	28 (56%)	22 (2-207)	37 (100%)	25 (68%)	13 (100%)	6 (46%)	1.00	0.20
Constitutional symptoms, N.									
Fatigue	21 (42%)	15 (30%)	42 (22-144)	13 (35%)	10 (27%)	8 (62%)	5 (38%)	0.12	0.08
Weight loss	15 (30%)	2 (4%)	47 (23-166)	9 (24%)	1 (3%)	6 (46%)	1 (8%)	0.26	0.35
Dermatological events, N.									
HFSR	31 (62%)	18 (36%)	20 (10-203)	27 (73%)	15 (41%)	4 (31%)	3 (23%)	0.02	0.68
Rash	12 (24%)	8 (16%)	8 (2-17)	8 (22%)	6 (16%)	4 (31%)	2 (15%)	0.71	0.63
Alopecia	8 (16%)	0	32 (16-42)	5 (14%)	0	3 (23%)	0	0.41	NA
Gastrointestinal events, N.									
Diarrhea	24 (48%)	13 (26%)	28 (16-207)	19 (51%)	12 (32%)	5 (38%)	1 (8%)	0.53	0.36
Nausea/vomiting	15 (46%)	0	26 (16-207)	8 (22%)	0	6 (46%)	0	0.15	NA
Constipation	2 (4%)	0	20	1 (3%)	0	1 (8%)	0	0.46	NA
Stomatitis	10 (20%)	0	22 (16-28)	6 (16%)	0	4 (31%)	0	0.42	NA
Arterial hypertension. N.	15 (30%)	3 (6%)	20 (10-75)	11 (30%)	3 (8%)	4 (31%)	0	1.00	NA
Any cardiovascular event, N.	2 (4%)	1 (2%)	12	0	0	2 (15%)	1 (8%)	0.06	0.19

*Listed are treatment-emergent adverse events, as defined by the National Cancer Institute Common Terminology Criteria (3.0), that occurred in at least 4% of patients); ****** Median (range); Mammalian Target of Rapamycin inhibitor (mTORi); Hand-foot skin reaction (HFSR); Not applicable (NA); §Chi-square/Fisher's exact test.

Table 3. Univariate and multivariate analysis of baseline predictors of overall survival*.

Features	Univariate analysis§		Multivariate analysis§	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Age, years**	1.0 (0.9-1.0)	0.61		
Male, N.	1.0 (0.4-2.4)	0.97		
Liver disease etiology at LT, N. (HCV vs non HCV)	1.0 (0.5-2.0)	0.97		
Native liver histology at LT, N.				
Milan-in	1.2 (0.6-2.4)	0.61		
Microvascular invasion	1.1 (0.5-2.1)	0.89		
Edmonson grade 3 or 4	0.9 (0.1-6.9)	0.92		
Time from LT to HCC recurrence**	0.99 (0.97-1.01)	0.29		
Time from HCC recurrence to SOR treatment**	0.99 (0.97-1.01)	0.34		
Baseline tumor extension, N. (Liver only *vs* other)	0.7 (0.2-2.5)	0.52		
AFP > 100 ng/mL at baseline, N.	2.5 (1.1-5.0)	**0.02**	1.6 (0.7-3.3)	0.29
HCC treatment with curative intent, N.	0.3 (0.2-0.7)	**0.003**	0.4 (0.2-1.0)	**0.04**
SOR + mTORi (*vs* SOR alone), N.	0.4 (0.2-0.9)	**0.04**	0.7 (0.3-1.7)	0.35

*Serum albumin and bilirubin were also analyzed without any significant results. **Median (range); Liver transplantation (LT); Hepatitis C virus (HCV); Hepatocellular carcinoma (HCC); sorafenib (SOR); Alpha-fetoprotein (AFP); Mammalian Target of Rapamycin inhibitor (mTORi); §Cox regression analysis.

Figure 1

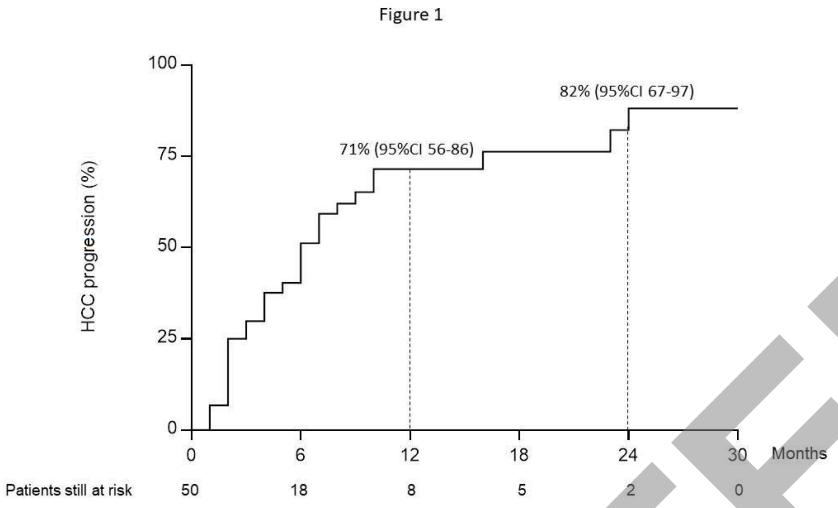

Figure 2

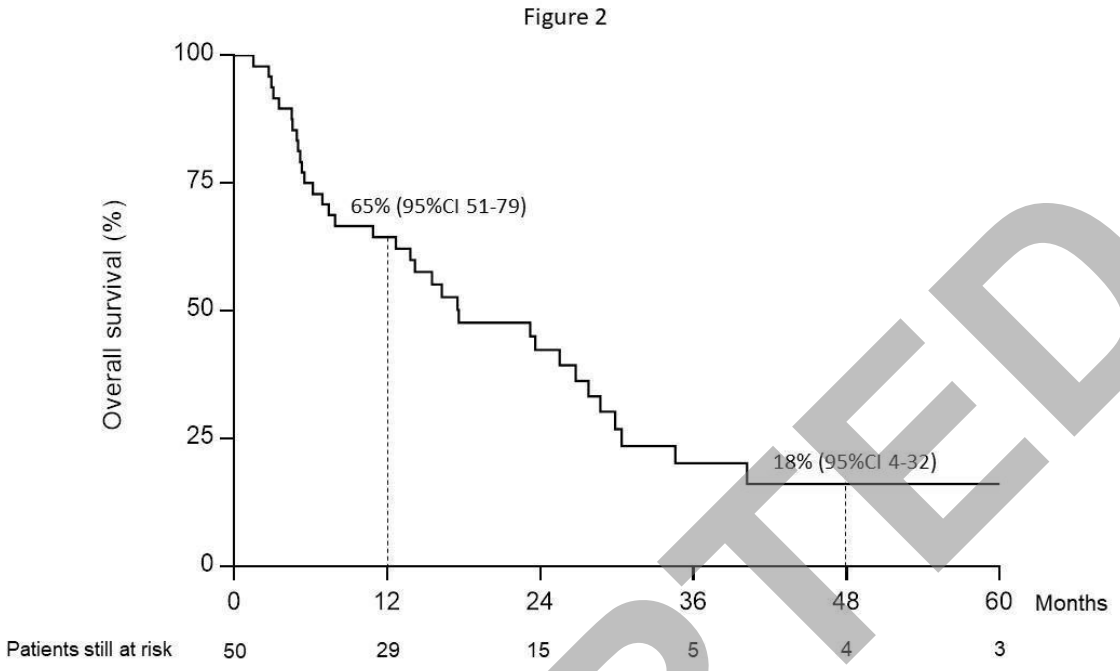

Figure 3

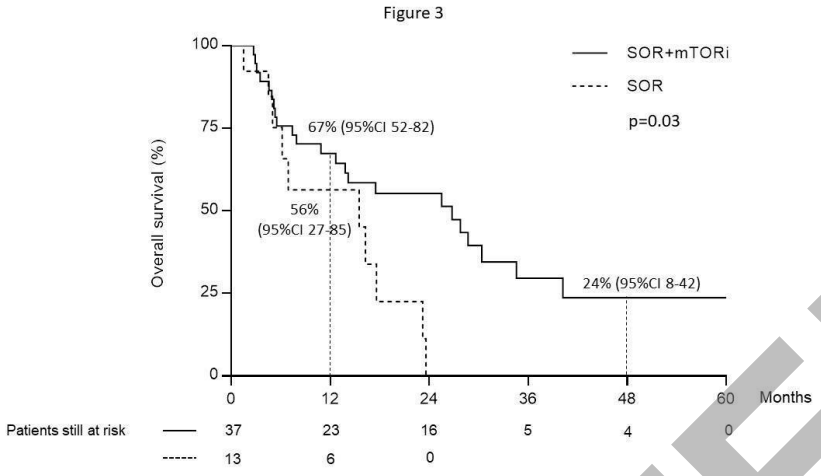

Figure 4