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Clinical Trial Results

Phase I Study Evaluating Dose De-escalation of Sorafenib with Metformin and Atorvastatin in Hepatocellular Carcinoma (SMASH)

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Abstract

Background: This phase I dose de-escalation study aimed to assess the tolerability, safety, pharmacokinetics (PK), and efficacy of sequentially decreasing doses of sorafenib in combination (SAM) with atorvastatin (A, 10 mg) and metformin (M, 500 mg BD) in patients with advanced hepatocellular carcinoma (HCC).

Methods: Patients were enrolled in 1 of 4 sequential cohorts (10 patients each) of sorafenib doses (800 mg, 600 mg. 400 mg, and 200 mg) with A and M. Progression from one level to the next was based on prespecified minimum disease stabilization (at least 4/10) and upper limits of specific grade 3-5 treatment-related adverse events (TRAE).

Results: The study was able to progress through all 4 dosing levels of sorafenib by the accrual of 40 patients. Thirty-eight (95%) patients had either main portal vein thrombosis or/and extra-hepatic disease. The most common grade 3-5 TRAEs were hand-foot-syndrome (grade 2 and grade 3) in 3 (8%) and transaminitis in 2 (5%) patients, respectively. The plasma concentrations of sorafenib peaked at 600 mg dose, and the concentration threshold of 2400 ng/mL was associated with higher odds of achieving time to exposure (TTE) concentrations >75% centile (odds ratio [OR] = 10.0 [1.67-44.93]; $P = .01$). The median overall survival for patients without early hepatic decompensation ($n = 31$) was 8.9 months (95% confidence interval [CI]: 3.2-14.5 months).

Conclusion: The SAM combination in HCC patients with predominantly unfavorable baseline disease characteristics showed a marked reduction in sorafenib-related side effects. Studies using sorafenib 600 mg per day in this combination along with sorafenib drug level monitoring can be evaluated in further trials.

(Trial ID: CTRI/2018/07/014865).

Key words: dose de-escalation; hepatocellular carcinoma; sorafenib; atorvastatin; metformin.

Lessons Learned

- The combination of sorafenib, atorvastatin, and metformin appears to be safe in advanced hepatocellular carcinoma.
- There is a marked reduction in sorafenib-related class-specific adverse events.
- The combination appears to have fair clinical activity in patients even with high-risk features.
- The dose of 600 mg sorafenib can be taken forward in clinical trials in combination with metformin and atorvastatin.

Discussion

Sorafenib is one of the recommended therapeutic options in advanced HCC, despite its causing significant toxicities, requiring dose reductions or cessation due to adverse events.[1-5] The rationale for combining metformin and atorvastatin with sorafenib in HCC includes the individual inhibitory effects of these drugs against chronic hepatitis and cirrhosis as well as their in vitro potential to re-sensitize HCC cells to the action of sorafenib.[6-10]

This phase I dose de-escalation study combining de-escalating doses of sorafenib with atorvastatin and metformin in patients with advanced hepatocellular carcinoma (HCC), to our

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Table 1. Patient characteristics at baseline.

Variable	*N* (%)
Median age (range)	55 (28-73)
Male gender	38 (95)
ECOG PS	
0	4 (10)
1	36 (90)
Child-Pugh	
A	32 (80)
B7	8 (20)
Barcelona Clinic liver cancer stage	
B	3 (7)
C	37 (93)
Status of liver disease	
Multifocal	22 (55)
Multicentric	24 (60)
Alpha-fetoprotein (ng/mL)	
Mean (range)	71 915 (0-1 266 318)
≥400 ng/mL	21 (53)
Presence of portal vein thrombosis, extrahepatic disease, or both	38 (95)
Portal vein thrombosis only	28 (70)
Extrahepatic disease only	20 (50)
Presence of varices at baseline	13 (33)
Etiology of HCC	
Hepatitis B	24 (60)
Hepatitis C	4 (10)
Alcoholic liver disease	5 (13)
Nonviral, nonalcoholic	7 (18)
Prior liver-directed therapy for HCC	8 (20)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma.

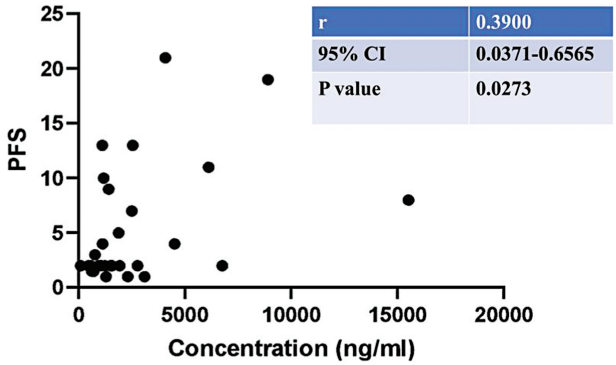

Figure 1. Correlation between the 3-hour sorafenib concentrations and time to progression. *r* = Spearman correlation. *P* < .05 is considered statistically significant.

knowledge, is the first of its kind in terms of prospectively assessing the safety and potential efficacy of the combination (Table 1). A relatively novel dose de-escalation design was used primarily because the design has been attempted with other anti-VEGF agents like sorafenib.[11,12] Second, the maximum tolerated dose (MTD) dose for sorafenib identified in phase I trials was 800 mg per day, but activity was seen at lower doses of 400 mg and 600 mg per day as well. Available clinical and preclinical data have suggested that the MTD doses of anti-angiogenic drugs may not coincide with their optimum biological doses (OBD). A dose de-escalation design helps to identify the OBD without compromising efficacy as long as predetermined efficacy criteria are followed.

A promising finding of the study was the excellent tolerance of the combination at all dosing levels of sorafenib. Expected class-specific sorafenib-related adverse events like HFS, diarrhea, and hypertension were uncommon as were other side effects and the need for dose modifications. This is possibly due to the addition of metformin and/or atorvastatin. Atorvastatin has been shown to regulate FasL expression in T cells, peripheral blood mononuclear cells, and human carotid atherosclerotic plaques and this potentially could result in a decreased incidence of side effects like HFS.

The steady-state plasma concentration of sorafenib in the study was proportional to the dose up to 600 mg BD beyond which both 3-hour and 6-hour concentrations decreased noticeably (Fig. 1). Our results showed a significant correlation between 3-hour steady-state levels of sorafenib and time to event (TTE). The 3-hour concentration cutoff of 2400 ng/mL was found to be associated with longer TTE without the higher risk of grade 3/4 toxicity. The dose of 600 mg per day allowed a high probability of patients to achieve this target concentration compared with other dose levels.

Despite a predominance of patients with adverse baseline characteristics like extrahepatic disease and portal vein thrombosis, the combination of drugs showed reasonable clinical activity. In patients without early hepatic decompensation, the median survival of 8.9 months is encouraging. Based on safety data as well as pharmacokinetics (PK) analysis, the dose of sorafenib that can be considered for further trials in advanced HCC is 600 mg daily when combined with 10 mg of atorvastatin and 500 mg sustained-release metformin twice daily.

Author disclosures and references available online.

Trial Information	
Disease	**Hepatocellular carcinoma**
Stage of disease/treatment	Metastatic/advanced
Prior therapy	None
Type of study	Phase I, dose de-escalation
Primary endpoints	Safety, recommended phase II dose
Secondary endpoints	Toxicity, pharmacodynamics, correlative endpoint
Investigator's analysis	Active and should be pursued further

Additional Details of Endpoints or Study Design

Trial Design

In this prospective open-label phase 1 dose de-escalation study, patients satisfying study criteria were sequentially accrued into 4 cohorts of 10 patients each (Table 2). Each cohort corresponded to a dose level of Sorafenib-Level 1—Sorafenib 800 mg plus Atorvastatin 10 mg OD (A) plus Metformin 500 mg BD (M), Level 2—Sorafenib 600 mg plus AM, Level 3—Sorafenib 400 mg plus AM, and Level 4—Sorafenib 200 mg plus AM. Patients were accrued in one dose level and accrual in the next dose level would only be allowed if the following criteria were met—achievement of disease stabilization (stable disease [SD]) or response (complete response [CR] and/or partial response [PR]) in at least 4 patients at the end of 2 months; less than 30% individual or 60% cumulative grade 4 or grade 5 intervention-related toxicities, specifically mucositis, diarrhea, hand-foot-syndrome, hepatitis or hyperbilirubinemia, cardiac dysfunction, febrile neutropenia, and thrombocytopenia; or requirement for dose reduction of Sorafenib in less than one-third patients, in that particular cohort. Patients received their planned treatment until unacceptable toxicities, loss of benefit as per defined response criteria or patient choice. Dose modifications were allowed as per predefined criteria.

Sorafenib Concentrations in Plasma

Plasma samples were collected at a steady-state between days 14 and 18 at 3 hours and 6 hours after the morning dose to measure sorafenib levels. Three milliliters of blood were collected in K2 EDTA vacutainer tubes and centrifuged at 3000 revolutions per minute (rpm) for 10 minutes to separate plasma. The separated plasma was stored at −80°C pending analysis. Sorafenib levels were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS).[13] Briefly, plasma proteins were precipitated with 0.1% formic acid in acetonitrile and an aliquot of the supernatant was dried, reconstituted with 30 µL of 50% methanol in water, of which 2 µL was injected into a reverse-phase chromatography system (SHIMADZU Nexera X2 Micro LC) consisting of a Kinetex 1.7 µm C18 100 Å, 100 × 3 mm LC Column. The stable isotope 13C-labeled sorafenib was used as an internal standard. The outlet of the column was connected to a triple quadruple mass spectrometer with electrospray ionization (AB SCIEX Q-TRAP 4500). Ions were detected in the positive mode using multiple reaction monitoring. The concentration of sorafenib was determined against a standard curve plotted across concentrations ranging from 0.05 to 10 µg/mL.

Drug Information: Arm 1	
Generic/working name	**Sorafenib**
Drug type	Small molecule
Drug class	Angiogenesis—VEGF
Dose	800 mg per flat dose
Route	oral (po)
Schedule of administration	800 mg per day
Generic/working name	**Metformin**
Drug type	Oral hypoglycemic
Drug class	Biguanide
Dose	500 mg per flat dose
Route	Oral (po)
Schedule of administration	500 mg sustained release twice daily
Generic/working name	**Atorvastatin**
Drug type	Lipid-lowering agent
Drug class	HMG-CoA Reductase Inhibitors
Dose	10 mg per day
Route	Oral (po)
Schedule of administration	10 mg per day

Drug Information: Arm 2	
Generic/working name	**Sorafenib**
Trade name	Sorafenib
Drug type	Small molecule
Drug class	Angiogenesis—VEGF
Dose	600 mg per flat dose
Route	Oral (po)
Schedule of administration	600 mg per day
Generic/working name	**Metformin**
Drug type	Oral hypoglycemic
Drug class	Biguanide
Dose	500 mg per flat dose
Route	Oral (po)
Schedule of administration	500 mg sustained release twice daily
Generic/working name	**Atorvastatin**
Drug type	Lipid-lowering agent
Drug class	HMG-CoA reductase inhibitors
Dose	10 mg per flat dose
Route	Oral (po)
Schedule of administration	10 mg per day

Drug Information: Arm 3	
Generic/working name	**Sorafenib**
Drug type	Small molecule
Drug class	Angiogenesis - VEGF
Dose	400 mg per flat dose
Route	Oral (po)
Schedule of administration	400 mg per day
Generic/working name	**Metformin**
Drug type	Oral hypoglycemic
Drug class	Biguanide
Dose	500 mg per flat dose
Route	Oral (po)
Schedule of administration	500 mg sustained release twice daily
Generic/working name	**Atorvastatin**
Drug type	Lipid-lowering agent
Drug class	HMG-CoA Reductase Inhibitors
Dose	10 mg per flat dose
Route	Oral (po)
Schedule of administration	10 mg per day

Drug Information: Arm 4	
Generic/working name	**Sorafenib**
Drug type	Small molecule
Drug class	Angiogenesis - VEGF
Dose	200 mg per flat dose
Route	Oral (po)
Schedule of administration	200 mg per day
Generic/working name	**Metformin**
Drug type	Oral hypoglycemic
Drug class	Biguanide
Dose	500 mg per flat dose
Route	Oral (po)
Schedule of administration	500 mg SR twice daily

Generic/working name	Atorvastatin
Drug type	Lipid-lowering agent
Drug class	HMG-CoA Reductase Inhibitors
Dose	10 mg per flat dose
Route	Oral (po)
Schedule of administration	10 mg per day

Dose De-escalation Table

Dose level	Dose of drug: sorafenib	Dose of drug: metformin	Dose of drug: atorvastatin	Number enrolled	Number evaluable for toxicity
1	800 mg	500 mg SR BD	10 mg	10	10
2	600 mg	500 mg SR BD	10 mg	10	10
3	400 mg	500 mg SR BD	10 mg	10	10
4	200 mg	500 mg SR BD	10 mg	10	10

Patient Characteristics

Number of patients, male	38
Number of patients, female	2
Stage	Metastatic/advanced
Performance Status: ECOG PS	0: 4 1: 36 2: 0 3: 0 Unknown: 0

Primary Assessment Method: Arm 1

Title	Activity
Number of patients screened	12
Number of patients enrolled	10
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10
Evaluation Method	RECIST 1.0
Response assessment CR	*n* = 0 (0%)
Response assessment PR	*n* = 0 (0%)
Response assessment SD	*n* = 5 (50%)
Response assessment PD	*n* = 1 (10%)
Response assessment, patients who had clinical disease progression prior to radiological evaluation	*n* = 4 (40%)
(Median) duration assessments TTP	2 months, CI: 0.4-3.6

Primary Assessment Method: Arm 2

Title	Clinical activity
Number of patients screened	13
Number of patients enrolled	10
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10
Evaluation Method	RECIST 1.0
Response assessment CR	*n* = 0 (0%)
Response assessment SD	*n* = 4 (40%)
Response assessment PD	*n* = 3 (30%)
Response assessment OTHER	*n* = 3 (30%)
(Median) duration assessments TTP	2.1 months, CI: 1.9-2.3

Primary Assessment Method: Arm 3

Title	Clinical
Number of patients screened	13
Number of patients enrolled	10
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10
Evaluation Method	RECIST 1.0
Response assessment CR	*n* = 0 (0%)
Response assessment PR	*n* = 0 (0%)
Response assessment SD	*n* = 4 (40%)
Response assessment PD	*n* = 2 (20%)
Response assessment OTHER	*n* = 4 (40%)
(Median) duration assessments TTP	2.8 months, CI: 1-3.3

Primary Assessment Method: Arm 4

Title	Clinical activity
Number of patients screened	14
Number of patients enrolled	10
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10
Evaluation Method	RECIST 1.0
Response assessment SD	*n* = 0 (0%)
Response assessment PD	*n* = 6 (60%)
Response assessment OTHER	*n* = 4 (40%)
(Median) duration assessments TTP	1.6 months, CI: 1-2.1

Adverse Events

There were no DLTs in the study. The major clinically relevant adverse events were (1) hand-foot syndrome (grade 2 and grade 3): 3 patients; (2) transamnitis (grade 3): 2 patients; and (3) diarrhea (grade 3): 1 patient

Pharmacokinetics/Pharmacodynamics

Dose level	Dose of drug: sorafenib	Dose of drug: metformin	Dose of drug: atorvastatin	Number with measured drug levels	Cmax (μg/L) mean ± SD
1	800	500 BD	10	10	2049.9 ± 2618.8
2	600	500 BD	10	8	4782.5 ± 4869.2
3	400	500 BD	10	7	1928.9 ± 1287.4
4	200	500 BD	10	8	1065 ± 687.4

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

This phase I dose de-escalation study combining de-escalating doses of sorafenib with atorvastatin and metformin in patients with advanced HCC, to our knowledge, is the first of its kind in terms of prospectively assessing the safety and potential efficacy of the combination. All the dose levels of sorafenib (800 mg, 600 mg, 400 mg, and 200 mg) appeared to be safe when combined with 10 mg tablet daily of atorvastatin and 500 mg sustained release tablets of metformin twice daily.

A majority of our patients had a number of poor prognostic factors in the form of Portal bein thrombosis (70%), AFP levels >400 ng/mL (53%), and hepatitis B. Hepatitis B-related HCC is known to have inferior outcomes with HCC.[14-16] Macrovascular invasion, especially, is associated with a dismal prognosis with median survivals ranging from 2 months to 5 months with various treatment modalities.[16-18] While the focus in developed countries has been directed toward drug discovery for the treatment of HCC, the focus in low–middle-income countries needs to be drug repurposing and the current combination of drugs is a step in that direction.[19]

Statins alone, specifically Pravastatin has been evaluated in combination with sorafenib in HCC with equivocal

improvements in efficacy outcomes.[20,21] However, the rationale for combining metformin and atorvastatin with sorafenib in HCC include the individual inhibitory effects of these drugs against chronic hepatitis and cirrhosis as well as their in-vitro potential to re-sensitize HCC cells to the action of sorafenib. Additionally, these medications are prime targets for drug repurposing in HCC, considering their pleiotropic actions as well as inexpensive nature and long-term safety data when used in other indications.

A promising finding of the study was the excellent tolerance of the combination at all dosing levels of sorafenib. Expected class-specific sorafenib-related adverse events like HFS, diarrhea, and hypertension were uncommon as were other side effects and need for dose modifications. A literature search with regards to mechanisms for atorvastatin or metformin reducing class side effects with tyrosine kinase inhibitors (TKIs) like sorafenib revealed some suggestions explaining this effect. One of the mechanisms for HFS caused by TKIs is Fas/Fas Ligand-mediated keratinocyte death.[22] Atorvastatin has been shown to regulate FasL expression in T cells, peripheral blood mononuclear cells, and human carotid atherosclerotic plaques.[23] Whether such regulation occurs in the skin and other mucosal membranes need further evaluation, though this can be mooted as a plausible explanation for the reduction in sorafenib-related side effects. Again, a combination of atorvastatin and polyprenol has been shown to reduce the incidence of capecitabine and 5-fluorouracil induced Palmar-plantar erythrodysesthesia (PPE). The purported mechanism of atorvastatin in reducing PPE is its inhibitory effects on cysteinyl leukotrienes and immunoglobulin E-dependent histamine release in human mast cells.[24] Whether a similar action is at work in reducing sorafenib-induced HFS needs evaluation.[25] The reduction in other class-specific side effects also needs similar evaluation.

We observed that steady-state plasma concentration of sorafenib was proportional to the dose up to 600 mg BD beyond which both 3-hour and 6-hour concentrations decreased noticeably. The 3-hour and 6-hour time points were chosen for drug level measurement because the time to maximum (T_{max}) concentration of sorafenib lies between 2 and 12 hours.[26,27] The average dose normalized plasma concentration of sorafenib with 800 mg BD dose was 68% and 75% less than that observed with 600 mg BD at 3 hours and 6 hours, respectively (Table 3). In dose-escalation studies, a less than proportional increase in area under the curve (AUC) and C_{max} was observed with increasing doses of sorafenib reaching a plateau at 400-600 mg BD.[28,29]

Our results showed a significant correlation between 3-hour steady-state levels and TTE (Figures 2–4). Additionally, the 3-hour concentration cutoff of 2400 ng/mL was found to be associated with longer TTE without a higher risk of grade 3/4 toxicity. However, the concentration of 2400 ng/mL at 3 hours is markedly lower than the threshold trough sorafenib concentration of 3450 ng/mL reported by Terada and colleagues to be associated with grade ≥ 3 toxicity.[30] The dose of 600 mg per day allows a high probability of patients to achieve this target concentration compared with other dose levels. A preclinical study by Szalek et al. showed that atorvastatin and metformin both significantly affect the AUC of sorafenib, albeit in different directions, when used concurrently. While atorvastatin increased the exposure to sorafenib by 66.6%, metformin significantly decreased the sorafenib AUC by 44%.[31] This is especially important in the current study since the exposure of sorafenib reported in our study is lower than that reported in other studies.[28,29,32] This could potentially be a result of drug–drug interaction with metformin and/or atorvastatin, resulting in balanced sorafenib exposure and improved tolerance with increasing doses as well. These findings, in combination with the safety and efficacy data, hint at hitherto unknown additional actions of metformin and atorvastatin at the cellular level beyond the reduction of sorafenib drug levels as indicated by the PK studies.

Besides the encouraging safety data, the study also suggests that the combination of sorafenib, atorvastatin, and metformin has activity in advanced HCC, though this requires evaluation in larger studies. In patients who were able to take a reasonable duration of the treatment without early hepatic decompensation (treatment taken beyond 1 month), the median survival of 8.9 months is encouraging and compares well with existing data in patients with multiple negative prognostic factors (Figs. 5, 6).

The PK analysis and efficacy data suggest that 600 mg sorafenib dosing per day schedule as part of the 3-drug combination can be taken forward for prospective studies as disease stabilization rates were similar to the higher doses with an equally acceptable safety profile. The addition of metformin and atorvastatin appears feasible and relevant, by virtue of their role in marked toxicity reduction and possible minimal additive action on the chronic hepatitis-cirrhosis-HCC disease spectrum. Disease stabilization or responses were not seen with 200 mg sorafenib dosing, though this dosing level also satisfied the safety criteria.

In conclusion, the combination of reducing doses of sorafenib with constant doses of atorvastatin and metformin shows a favorable safety profile in patients with advanced HCC with a definite reduction in sorafenib-related class-specific side effects. The efficacy data also appear promising. Based on the safety data as well as PK analysis, the dose of sorafenib that can be considered for further trials in advanced HCC is 600 mg daily when combined with 10 mg of atorvastatin and 500 mg sustained-release metformin twice daily, especially in the type of patients' cohort we enrolled.

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Conflict of Interest

Vikas Ostwal: Reddy's Lab Pvt Ltd., Cadila Pharmaceuticals Pvt Ltd. (RF [institutional]). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures and Tables

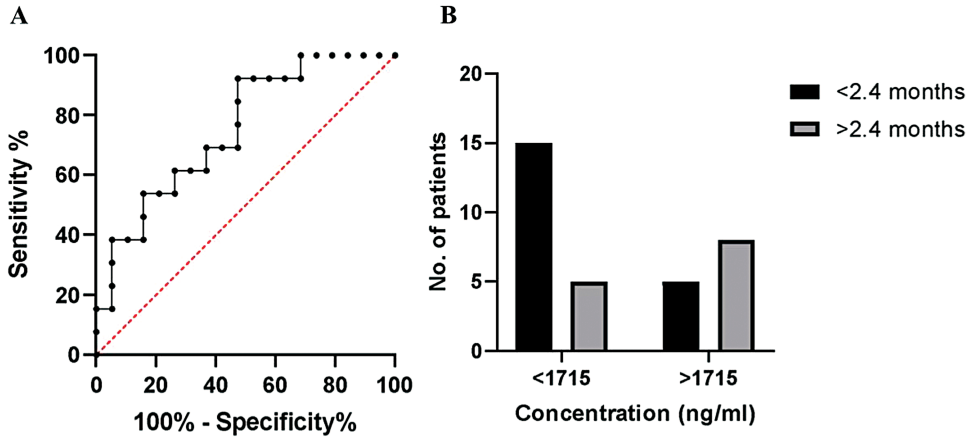

Figure 2. (**A**) Receiver operating characteristics curve showing the discriminatory potential of 3-hour steady-state sorafenib concentration to identify patients with time to progression (TTP) longer or shorter than the median TTP of 2.4 months (AUC = 0.75 [0.58-0.92]; *P* = .017). The concentration of 1715 ng/mL had the most optimal sensitivity and specificity of 61.5% and 73.7%, respectively to predict the TTP of at least 2.4 months. (**B**) The relationship between the threshold 3-hour steady-state plasma sorafenib concentration of 1.715 ng/mL and the duration of TTP. The odds ratio of having the TTP of at least 2.4 months at this threshold concentration was 4.8 (1.04-18.4), *P* = .067. *P* < .05 is considered statistically significant.

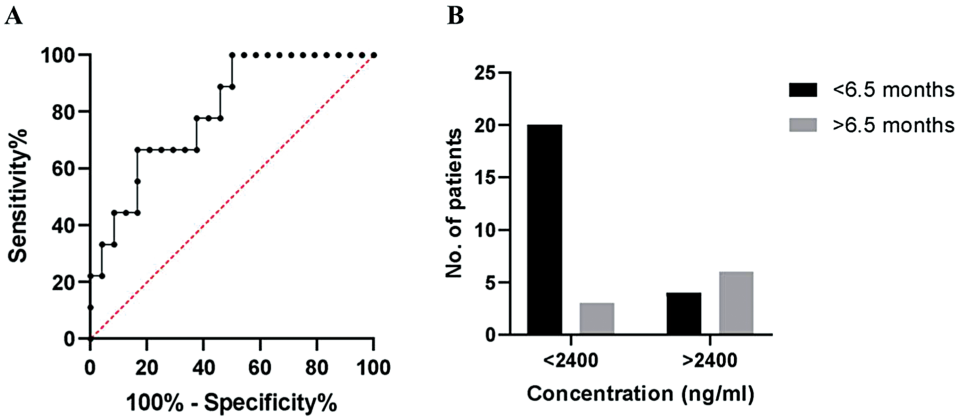

Figure 3. (**A**) Receiver operating characteristics curve showing the discriminatory potential of 3-hour steady-state sorafenib concentration to identify patients with time to progression (TTP) longer or shorter than the 75 percentile TTP of 6.5 months (AUC = 0.80 [0.64-0.96]; *P* = .009). The concentration of 2400 ng/mL had the most optimal sensitivity and specificity of 66.7% and 83.3%, respectively to predict the TTP of at least 6.5 months. (**B**) The relationship between the threshold 3-hour steady-state plasma sorafenib concentration of 2400 ng/mL and the duration of TTP. The odds ratio of having the TTP of at least 6.5 months at this threshold concentration was 10 (1.67-44.9), *P* = .01. *P* < .05 is considered statistically significant.

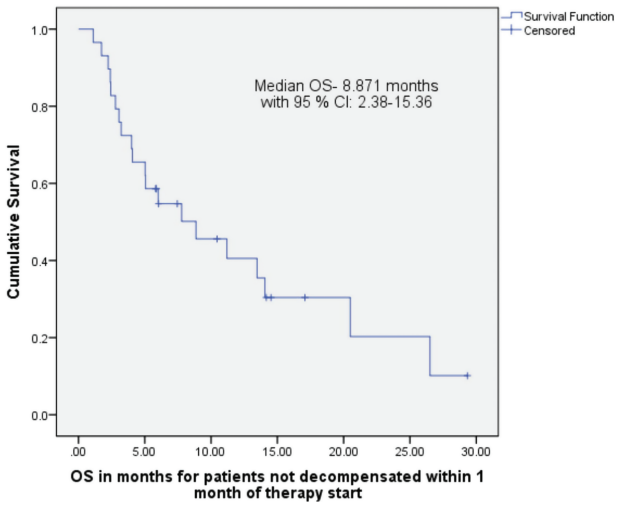

Figure 4. Bar diagram for time to event and overall survival of entire study population.

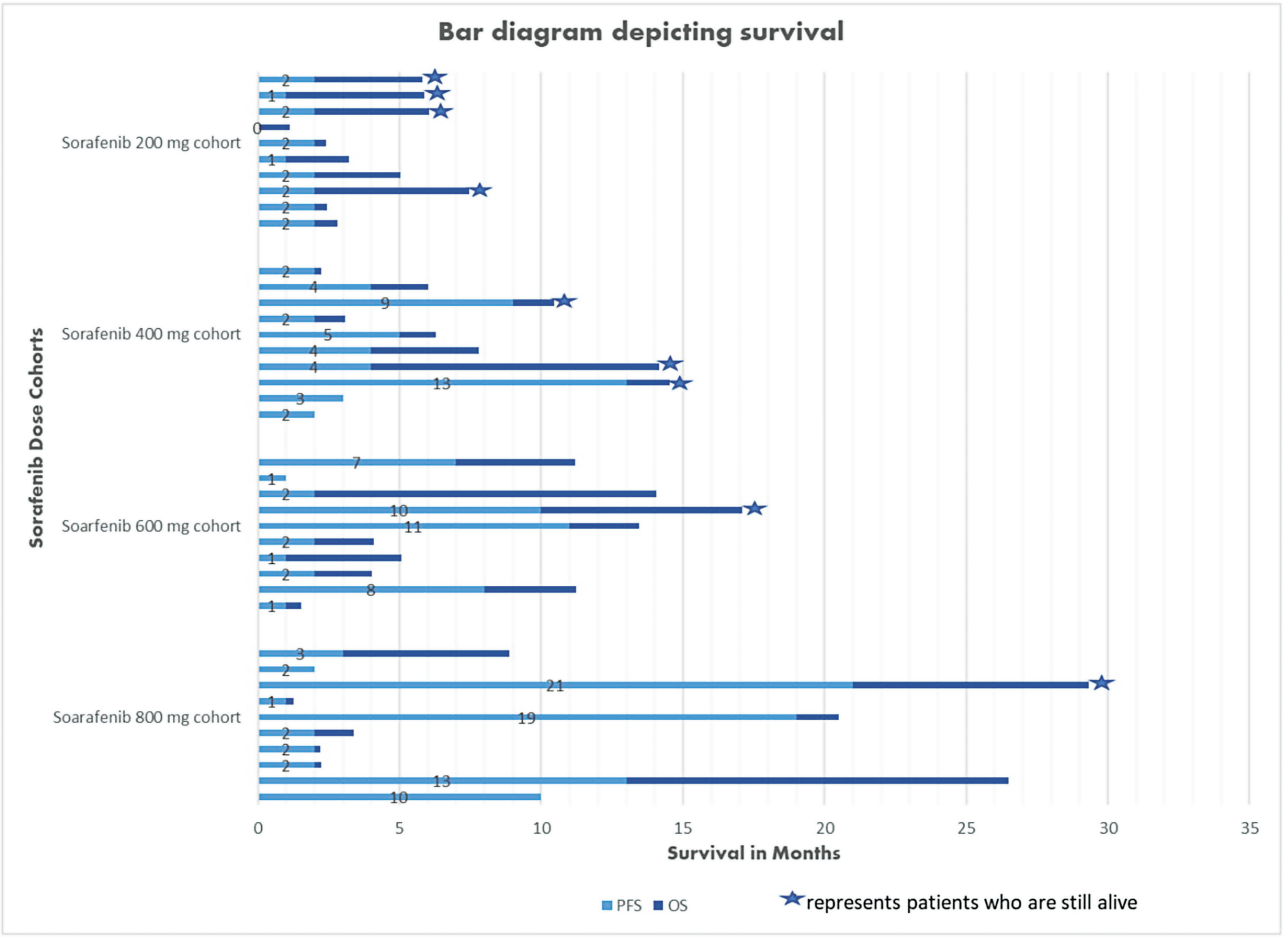

Figure 5. Dose normalized sorafenib concentrations.

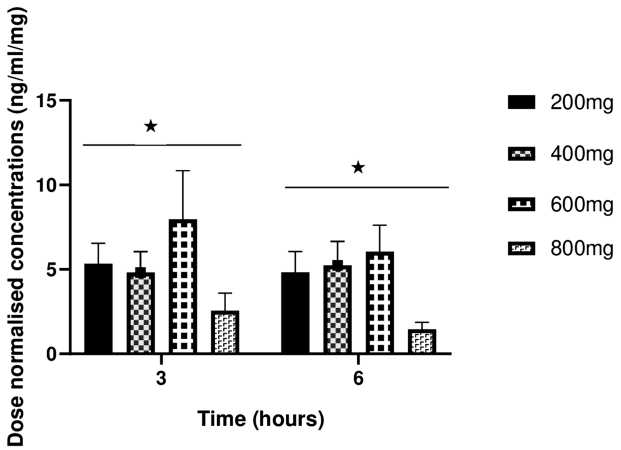

Figure 6. Median overall survival for patients who did not undergo early hepatic decompensation.

Table 2. Comparison of individual dose cohorts.

Variable	Cohort 1 (n = 10)	Cohort 2 (n = 10)	Cohort 3 (n = 10)	Cohort 4 (n = 10)	Entire cohort (n = 40)
Best radiological response					
Response (complete or partial)	0	0	0	0	0
Stable disease	5	4	4	0	13
Progressive disease	1	3	2	6	24
Response not assessed	4	3	4	4	11
Reason for treatment cessation					
Disease progression	6	7	4	10	25
Liver decompensation	4	3	2	0	9
Others	0	0	2	0	2
Grade 3 and grade 4 adverse events	1	1	1	0	3
Hand-foot-syndrome (Grade 2 and 3)					
Hypertension	0	0	0	0	0
Transaminitis	0	1	1	0	2
Nausea and vomiting	0	1	0	0	0
Diarrhea	1	0	0	0	1
Requirement for dose modifications/interruption	1	2	2	1	6
On treatment	0	0	2	0	2

Table 3. Steady-state plasma concentrations of sorafenib for the 4 dose cohorts at 3 and 6 hours, respectively.

Time point	Dose	200 mg (N = 8)	400 mg (N = 7)	600 mg (N = 8)	800 mg (N = 10)
Concentration (ng/mL)					
3 h	Mean	1065.0	1928.9	4782.5	2049.9
	SD	687.4	1287.4	4869.2	2618.6
6 h	Mean	965.5	2098.6	3627.1	1167.0
	SD	693.2	1489.9	2668.6	1030.0