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ORIGINAL ARTICLE

Efficacy of regorafenib in the second-and third-line setting for patients with advanced hepatocellular carcinoma: A real life data of multicenter study from Turkey

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Summary

Purpose: *After failure of the first-line sorafenib treatment in advanced or metastatic stage hepatocellular carcinoma (HCC), regorafenib is one of the newly-approved targeted agents. We aimed to evaluate the efficacy of regorafenib in patients with advanced HCC treated in the second- or third-line setting.*

Methods: *In this retrospective and multicenter study, advanced HCC patients not eligible for local therapies, who received a second- or third-line regorafenib therapy after progression on the first-line sorafenib or sequential therapy with chemotherapy (CT) followed by sorafenib, were included.*

Results: *In the first-line setting, 28 (28.9%) patients received CT and 69 (71.1%) patients received sorafenib. There were 24 (24.7%) patients who were intolerant to sorafenib. Disease control rate (DCR) was 53.6% for all patients treated with regorafenib, 62.3% in patients who received regorafenib in the second-line, and 32.1% for those receiving regorafenib in the third-line (p=0.007). Median progression-free survival (PFS) and overall survival (OS) were 5.6 (range; 4.3-6.9) and 8.8 (range, 6.3-11.3) months for all patients treated with regorafenib vs. 7.1 months and 10.3 months for patients who received regorafenib in the second-line vs. 5.1 and 8.7 months for patients who received regorafenib in the third-line, respectively; however, there was no statistically significant difference (p_{PFS}=0.22 and p_{OS}=0.85).*

Conclusion: *Although receiving CT as a first-line therapy in advanced HCC patients did not affect the survival rates of subsequent regorafenib therapy, it might diminish the DCR of regorafenib.*

Key words: *hepatocellular carcinoma, regorafenib, disease control rate, overall survival, chemotherapy, anti-VEGF therapy*

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and one of the leading causes of cancer-related deaths. It usually develops in a setting of chronic liver injury by various etiologies of chronic liver disease [1,2]. Today, surgical resection and liver transplantation are the main curative treatment strategies for patients with early stage HCC. Patients not candidate for surgical resection or liver transplantation can be treated with local treatments as alternative options to curative strategies [3]. Nonetheless, recurrence is inevitable in most cases and treatment with a curative intent is unfortunately not feasible at initial diagnosis.

Response to cytotoxic chemotherapy (CT) is poor in patients with advanced or metastatic HCC, with significant toxicity as well as lack of survival benefit [4]. After the Sharp study in 2008, sorafenib, a multi-targeted tyrosine-kinase inhibitor (TKI) with a predominant anti-angiogenic activity, became the standard systemic treatment option in the first-line setting of advanced HCC patients with Child-Pugh class A [5]. After failure of the first-line sorafenib treatment in advanced or metastatic stage HCC, novel TKIs such as regorafenib, ramucirumab and cabozantinib are the newly approved targeted agents, with significant overall survival (OS) and progression-free survival (PFS) benefits. The randomized phase III REACH-2 trial demonstrated PFS and OS advantages with ramucirumab in advanced HCC patients with α-fetoprotein (AFP) level >400 ng/mL who progressed on sorafenib treatment. Although, ramucirumab is the currently-approved drug by the Food and Drug Administration (FDA), it is not yet used widely [6].

In many countries, regorafenib and cabozantinib are the other FDA-approved TKIs and currently used in advanced HCC patients not appropriate for locoregional therapies after progression on sorafenib therapy. Although both drugs are used in advanced HCC patients after failure of sorafenib therapy, the phase III RESORCE study of regorafenib did not include patients with advanced HCC patients if they had received any systemic treatment other than sorafenib [7]. In contrast, the phase III CELESTIAL study of cabozantinib allowed to include advanced HCC patients who had progressed on systemic CT or sorafenib therapy [8]. As a result of these studies including advanced HCC patients, regorafenib is used as a second-line treatment option after progression on sorafenib treatment. On the other hand, cabozantinib is used in the second- or third-line setting after failure of sorafenib and/or other systemic therapies. In real-life experience, regorafenib can be used in the third-line setting in advanced HCC patients who received CT in the first-line setting followed by a subsequent sorafenib treatment. Due to the fact that no data regarding the efficacy of regorafenib in HCC patients in the third-line setting is currently available, we aimed to compare the efficacy of regorafenib in advanced HCC patients treated in the second- and the third-line settings.

Methods

Study design

A total of 21 medical oncology clinics from different regions of Turkey participated in this retrospective-multicenter study. The medical records of HCC patients,

Table 1. Demographic and clinical characteristics

Characteristics	*n (%)*
Age, years	
Median	61
Interquartile range	58-68
Gender (female or male)	19/78
ECOG PS	
0-1	84 (86.6)
2	13 (13.4)
BCLC	
B	46 (47.4)
C	51 (52.6)
Extrahepatic metastasis	51 (52.6)
Lymph node	22 (22.6)
Lung	19 (19.5
Bone	11 (11.3)
Surrenal	2 (2.1)
Macrovascular invasion	38 (39.2)
Cirrhosis	43 (44.3)
Etiology	
HBV	55 (56.7)
HCV	9 (9.3)
Alcohol	2 (2.0)
Unknown	31 (32.0)
AFP level (ng/mL)	
<400	45 (53.6)
≥400	39 (46.4)
Sorafenib intolerance	24 (24.7)
First-line chemotherapy	28 (28.9)
Anthracycline	12 (42.9)
GEMOX	10 (35.8)
5-Fluorouracil-based	5 (17.8)
Cisplatin+gemcitabine	1 (3.5)

AFP: alpha feto protein, BCLC: Barcelona Clinic Liver Cancer, ECOG: eastern cooperative oncology group, GEMOX: gemcitabine-oxaliplatin, HBV: hepatitis B virus, HCV: hepatitis C virus

who admitted to oncology outpatient clinics from 2015 through 2019, were analyzed. Finally, 97 patients with advanced HCC not eligible for surgical or local treatments who received regorafenib in the second- or third-line settings were included in the analysis. The diagnosis of HCC was based on the histopathological and/or imaging study findings. The clinical and demographical features including age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), Barcelona Clinic of Liver Cancer (BCLC) score, extrahepatic metastasis, macrovascular invasion, cirrhosis, AFP level, sorafenib tolerance, and whether or not the first-line treatment was chemotherapy were recorded. The diagnosis of cirrhosis in the setting of a chronic liver disease was based on histopathological results, clinical or laboratory findings, and imaging studies (e.g. ultrasound, AFP level).

Table 2. Disease control rates

	Chemotherapy *n (%)*	*Sorafenib* *n (%)*	*Regorafenib* *n (%)*
Partial response	4 (14.3)	17 (17.5)	9 (9.3)
Stable disease	4 (14.3)	49 (50.5)	43 (44.3)
Progressive disease	20 (71.4)	31 (32.0)	45 (46.4)

Table 3. Univariate and multivariate analyses for disease control rate in patients who received regorafenib

	Disease control rate					
	Univariate analysis			*Multivariate analysis*		
	HR	*95%CI*	*P*	*HR*	*95%CI*	*P*
Age, years						
<60	1.05	(0.47-2.35)	0.89	1.08	(0.42-2.81)	0.86
≥60	0.94	(0.42-2.10)		0.91	(0.35-2.38)	
Gender						0.33
Female	0.95	(0.34-2.60)	0.92	0.54	(0.15-1.86)	
Male	1.05	(0.38-2.86)		1.84	(0.53-6.32)	
ECOG PS			0.24			-
0-1	2.03	(0.61-6.73)		-	-	
2	0.49	(0.15-1.63)				
BCLC			0.58	1.68	(0.57-4.88)	0.34
B	1.25	(0.56-2.78)		0.59	(0.20-1.72)	
C	0.80	(0.35-1.78)				
Extrahepatic metastasis			0.27			0.31
No	0.27	(0.28-1.43)		0.57	(0.19-1.71)	
Yes	1.55	(0.69-3.48)		1.74	(0.58-5.20)	
Macrovascular invasion			0.27			0.42
No	0.63	(0.27-1.44)		0.66	(0.23-1.84)	
Yes	1.58	(0.69-3.62)		1.51	0.54-4.22)	
Cirrhosis			0.09			0.02
No	1.98	(0.88-4.47)		3.34	(1.20-9.29)	
Yes	0.50	(0.22-1.13)		0.29	(0.10-0.83)	
AFP ng/mL			0.98			0.48
<400	0.99	(0.43-2.27)		0.69	(0.25-1.91)	
≥400	1.01	(0.44-2.31)		1.43	(0.52-3.92)	
Sorafenib tolerance			0.59			0.96
Tolerant	0.77	(0.30-1.97)		1.02	(0.33-3.16)	
Intolerant	1.28	(0.50-3.27)		0.97	(0.31-3.00)	
First-line chemotherapy			0.007			0.006
No	3.49	(1.37-8.85)		4.97	(1.57-15.75)	
Yes	0.28	(0.11-0.72)		0.20	(0.06-0.63)	

AFP: alpha fetoprotein, BCLC: Barcelona Clinic Liver Cancer, ECOG: Eastern Cooperative Oncology Group, GEMOX: gemcitabine-oxaliplatin, HBV: hepatitis B virus, HCV: hepatitis C virus

Ethical approval

This study was conducted after obtaining the ethical approval from the Local Research Ethics Committee of Trakya University School of Medicine, with decision number 2019/1895. All procedures and stages in this multicenter and retrospective study were carried out in line with the World Medical Association Declaration of Helsinki, "Ethical Principles for Medical Research Involving Human Subjects", modified in October 2013.

Response evaluation

Disease control rate (DCR) was defined as the sum of percentages of advanced HCC patients achieving partial response (PR) and stable disease (SD) with regorafenib treatment (DCR:PR+SD). Sorafenib intolerance was defined as lowering the drug dose below 400 mg/day or discontinuation of sorafenib due to dose-limiting toxicity.

Statistics

Data were presented as median (25^{th}-75^{th} interquartile range). Categorical variables were reported as frequencies and group percentages. PFS and OS values were estimated using the Kaplan–Meier method. Possible factors associated with survival which were identified in univariate analysis were subsequently evaluated in a multivariate logistic regression analysis in an attempt to determine the independent predictors of DCR, which was adjusted for the age, gender, BCLC score, extrahepatic metastasis, macrovascular invasion, cirrhosis, AFP level, sorafenib tolerance, and presence of first-line CT. P value less than 0.05 was considered as statistically significant. PFS was defined as the time from the date of regorafenib initiation to the date of progression or death due to any cause. OS was calculated as the time from the date of regorafenib initiation to the date of death due to any reason or lost to follow-up.

Results

Of the 97 patients, 78 (80.5%) were male and 19 (19.5%) female, with a median age of 61 (range, 58-68). Only 13 (13.4%) patients had ECOG PS 2. The clinical and demographic features are shown in Table 1.

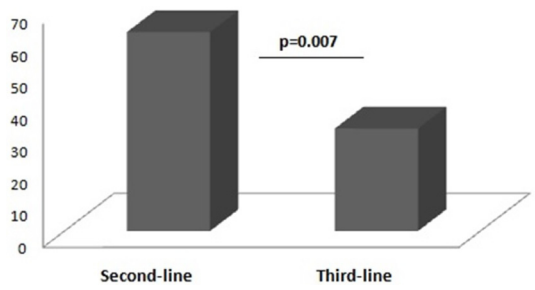

Figure 1. Response rates of regorafenib after progression on sorafenib in patients who received vs. not received first-line chemotherapy.

The number of patients who received chemotherapy vs. sorafenib in the first-line setting were 28 (28.9%) vs. 69 (70.1%), respectively. After progression on first-line CT, the patients received sorafenib in the second-line setting. There were 24 (24.7%) patients who were intolerant to sorafenib therapy. The median duration of treatment in the first-line setting was 2.1 months (interquartile range, 1.6-4.1) for CT compared to 6.2 months (interquartile range, 3.2-10.3) for sorafenib. After progression on the first-line CT or first-line sorafenib, the median duration of regorafenib treatment was 4.1 months (interquartile range, 2.6-7.3). The median duration of regorafenib therapy was 4.1 months (interquartile range 2.6-5.8) in patients who received upfront CT compared to 3.8 months (inter quantile range 2.3-7.5) in those who received sorafenib in

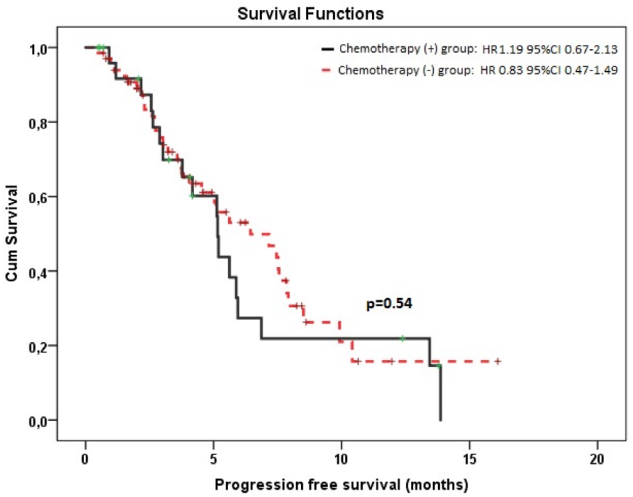

Figure 2. Progression-free survival of regorafenib patients who received chemotherapy or did not received chemotherapy in the first-line setting.

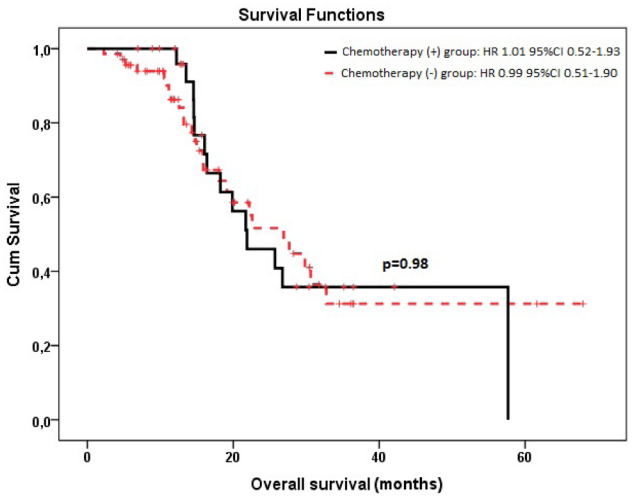

Figure 3. Overall survival of regorafenib patients who received chemotherapy or not in the first-line setting.

the first-line setting, with no significant difference (p=0.91). The DCR was 28.6% with CT and 68% with sorafenib treatment, whereas it was 53.6% for all patients who received regorafenib in the second- and third-line setting (Table 2). The DCR in patients treated with regorafenib who received a first-line CT was 62.3% vs. 32.1% in those not receiving first-line CT, with a statistically significant difference (p=0.007) (Figure1). There was no significant relationship between response to first-line CT and response to third-line regorafenib treatment (p=0.69). In addition, the response to regorafenib treatment was independent of the response to prior sorafenib treatment (p=0.25). Univariate analysis showed that there was no significant relation between DCR and clinical and demographic characteristics of the patients. In addition, multivariate analysis revealed that DCR was better in patients without cirrhosis compared to those with cirrhosis (p=0.02). On the other hand, DCR with regorafenib in patients who received CT in the first-line was worse than those receiving sorafenib in the first-line (p=0.006) (Table 3). Median PFS in all patients treated with regorafenib was 5.6 months (4.3-6.9). Median PFS of the patients who received first-line CT was 5.1 months (range, 3.6-6.6) [HR 1.38 (95% CI; 0.81-2.36)] compared to 7.1 months (range, 4.4-9.8) [HR 0.72 (95% CI; 0.42-1.23)] in those not receiving first-line CT, but this was not statistically significant (p=0.22) (Figure 2). Median PFS was better in patients with ECOG-PS 0-1 than those with ECOG-PS 2 (5.9 months vs. 3.0 months, respectively, p=0.04). There was not any significant relationship between PFS and age, gender, sex,

Table 4. Progression-free survival

Factors	*Median PFS (95%CI)*	*p value*
Age, years		
<60	5.6 (4.1-7.1)	0.74
≥60	5.0 (0.9-9.1)	
Gender		0.90
Female	6.8 (2.2-11.4)	
Male	5.1 (4.2-6.1)	
ECOG PS		0.04
0-1	5.9 (3.9-7.9)	
2	3.0 (1.8-4.2)	
BCLC		0.80
B	5.1 (3.8-6.4)	
C	6.4 (3.8-9.0)	
Extrahepatic metastasis		0.75
No	5.0 (3.8-6.3)	
Yes	6.8 (4.3-9.3)	
Macrovascular invasion		0.32
No	6.4 (4.3-8.4)	
Yes	5.0 (3.8-6.1)	
Cirrhosis		0.65
No	5.6 (3.9-7.2)	
Yes	5.0 (1.6-8.4)	
AFP level (ng/mL)		0.95
<400	5.9 (3.3-8.4)	
≥400	5.1 (4.7-5.4)	
Sorafenib tolerance		0.83
Tolerant	5.6 (3.9-7.2)	
Intolerant	5.6 (4.5-6.6)	
First-line chemotherapy		0.22
No	7.1 (4.4-9.8)	
Yes	5.1 (3.6-6.6)	

AFP: alpha fetoprotein, BCLC: Barcelona Clinic Liver Cancer, ECOG PS: Eastern Cooperative Oncology Group

Table 5. Overall survival

Factors	*Median OS (95%CI)*	*p value*
Age, years		
<60	8.5 (7.2-9.7)	0.68
≥60	10.3 (5.3-15.3)	
Gender		0.32
Female	14.1 (1.0-28.4)	
Male	8.7 (5.1-12.3)	
ECOG-PS		0.001
0-1	10.3 (8.0-12.6)	
2	4.0 (2.6-5.5)	
BCLC		0.23
B	9.8 (6.6-13.1)	
C	8.4 (5.3-11.5)	
Extrahepatic metastasis		0.99
No	7.8 (4.7-11.0)	
Yes	9.8 (7.5-12.1)	
Macrovascular invasion		0.22
No	10.7 (7.8-13.7)	
Yes	6.3 (2.7-9.8)	
Cirrhosis		0.02
No	10.6 (7.8-13.4)	
Yes	6.3 (4.7-7.8)	
AFP ng/mL		0.31
<400	10.3 (7.5-13.1)	
≥400	6.2 (4.6-7.8)	
Sorafenib tolerance		0.66
Tolerant	8.8 (4.7-12.9)	
Intolerant	8.7 (7.4-10.1)	
First-line chemotherapy		0.85
No	10.3 (6.2-14.4)	
Yes	8.7 (5.4-11.9)	

AFP: alpha fetoprotein, BCLC: Barcelona Clinic Liver Cancer, ECOG: Eastern Cooperative Oncology Group

prognostic factors of HCC, and prior sorafenib tolerance (Table 4). Median OS was 8.8 months (range, 6.3-11.3) for all patients who received regorafenib. Patients treated with first-line CT had median OS of 8.7 months (5.4-11.9) [HR 1.05 (95% CI; 0.57-1.93)] compared to 10.3 months (7.5-13.1) [HR 0.94 (95% CI; 0.51-1.73)] in those not receiving first-line CT; however, this was not significant (p=0.85) (Figure 3). Although p values for age, sex, ECOG PS and cirrhosis were <0.05 in univariate analysis, multivariate analysis showed that there was no significant difference between OS and these factors. Moreover, there was no statistically significant association between OS and other prognostic factors of HCC and prior sorafenib tolerance (Table 5).

Discussion

Sorafenib is the standard first-line treatment option for advanced HCC patients not appropriate for surgical or local treatments. However, CT can still be used prior to sorafenib therapy depending on the individual arrangements of health authorities and/or physician choices, although the response rates of cytotoxic CT in HCC are very low. In addition, the RESOURCE study included advanced HCC patients who had disease progression on first-line sorafenib treatment. Currently, there is no clear data regarding whether the efficacy of regorafenib treatment in advanced HCC patients who received CT in the first-line setting is similar to those who received sorafenib in the first-line setting [7]. Unlike the RESOURCE study, we analyzed the efficacy of regorafenib in patients with advanced HCC both in the second- and third-line setting who progressed on first-line CT or sorafenib therapy. The RESOURCE study evaluating regorafenib treatment in the second-line setting included advanced HCC patients with Child-Pugh score A, who progressed on sorafenib therapy. Sorafenib tolerance was defined as being able to use the drug ≥ 20 days and ≥ 400 mg/day in a-28-day period. In the same study, the median OS and PFS for regorafenib were 10.6 months (95% CI 9.1-12.1) and 3.1 months (95% CI 2.8-4.2), respectively, with a DCR of 65% [7]. Similarly, in our study, it was shown that median OS and DCR in patients who received regorafenib in the second-line setting after a progression on first-line sorafenib therapy were 10.3 months and 62.3%, respectively. However, PFS results in our study appear to be longer than those reported in the RESOURCE study. In addition, in our study DCR with regorafenib treatment was significantly better in advanced HCC patients treated in the second-line setting after progression on first-line sorafenib therapy. Median PFS and OS were shorter in advanced HCC patients who received regorafenib in the third-line setting although this finding did not reach statistical significance.

Recently, the randomized, placebo-controlled, phase III CELESTIAL trial evaluating the efficacy of cabozantinib in the second- or third-line treatment of patients with advanced HCC, the median OS and PFS were 10.2 and 5.2 months, respectively. There were 130 (28%) patients who received a first-line systemic CT prior to sorafenib treatment. In subgroup analysis, the median OS was 11.3 months in patients who received cabozantinib in the second-line setting compared to 8.6 months in patients who received cabozantinib in the third-line setting, with PFS values of 5.5 vs. 3.7 months, respectively. The DCR with cabozantinib therapy was 64% (n=300); however, the study lacked the results regarding the relationship between DCR and previous systemic treatments [11]. Our results regarding the use of regorafenib in the second- and third-line setting of advanced HCC patients were quite similar to those reported in the CELESTIAL study, which evaluated the efficacy of cabozantinib therapy in the second- or third-line setting. In view of these findings, it may be concluded that regorafenib and cabozantinib, which are the standard treatment options in the second-line setting after progression on sorafenib, can also show similar activity in the third-line treatment of advanced HCC. Numerical differences were found in OS and PFS depending on the use of regorafenib in the second-line vs. third-line setting, but these results were not statistically significant as observed in the CELESTIAL study, although this finding showed that the efficacy of cabozantinib in patients who received first-line CT was likely to be independent of CT. As a novel data, we showed that OS, PFS and DCR with regorafenib in patients who received first-line CT prior to sorafenib treatment was significantly worse than in patients who received sorafenib in the first-line, as shown in the CELESTIAL study. This difference might be explained by receiving an upfront CT that may partially limit the efficacy of regorafenib and cabozantinib. In particular, the significant difference in DCR observed in our study, supports this conclusion. RESOURCE and REACH-2 trials did not include sorafenib-intolerant patients [9-11]. In real-life, physicians may also encounter such patients. In our study the rate of sorafenib-intolerant patients was 24.7%.

In the present study, there was no significant relationship between sorafenib intolerant and sorafenib tolerant patients in terms of PFS and OS. We demonstrated that the efficacy of regorafenib appeared to be independent of sorafenib tolerance.

For the first time in the literature, we showed that the efficacy of regorafenib in the sorafenib-intolerant group was similar to that of the sorafenib-tolerant patients. In advanced or metastatic HCC, while sorafenib has already been shown to be effective in the first-line setting, it is not possible to conduct randomized prospective studies to evaluate the effect of cytotoxic CT on regorafenib efficacy. Therefore, real-life data which reflect the efficacy of regorafenib in advanced HCC patients who received first-line cytotoxic CT can help physicians to guide identifying the optimal treatment sequence.

The major limitations in our study were as follows: first, it was a retrospective study, hence having a likelihood of including potential biases that might have affected the study results; second, the number of patients receiving a first-line CT was relatively low; third, because the data were collected from different centers, it is not known whether or not the RECIST criteria were optimally applied during response evaluation by imaging methods. Despite all these limitations, the major strength of this study was that patients who received regorafenib in the second-line setting had better response than those receiving regorafenib in the third-line setting (DCR; 62.3% vs. 32.1%, respectively). To the best of our knowledge, this is the first study to demonstrate possible hazardous effect of CT on regorafenib efficacy in patients with advanced HCC. Further studies including larger sample size which reflect the real-life data are needed to clarify the possible relationship of sorafenib intolerance and effect of first-line CT on the efficacy of regorafenib after progression on sorafenib treatment.

In conclusion, systemic CT as a first-line treatment option may partially diminish the DCR of regorafenib; however, regorafenib can be used as an effective agent in the third-line setting.

Conflict of interests

The authors declare no conflict of interests.

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