

SPECIAL REPORT

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Refining sorafenib therapy: lessons from clinical practice

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ABSTRACT: Understanding the best use of sorafenib is essential in order to maximize clinical benefit in hepatocellular carcinoma. Based on Phase III and noninterventional study data, as well as our extensive experience, we discuss dose modification in order to manage adverse events, disease response evaluation and how to maximize treatment benefit. Sorafenib should be initiated at the approved dose (400 mg twice daily) and reduced/interrupted as appropriate in order to manage adverse events. Dose modification should be considered before discontinuation. Appropriate tumor response assessment is critical. Focusing on radiologic response may result in premature sorafenib discontinuation; symptomatic progression should also be considered. If second-line therapies or trials are unavailable, continuing sorafenib beyond radiologic progression may provide a clinical benefit. Our recommendations enable the maximization of treatment duration, and hence clinical benefit, for patients.

It is well established that hepatocellular carcinoma (HCC) is a complex and heterogeneous disease that is affected by multiple genetic and epigenetic alterations [1]. In the overwhelming majority of patients, liver cirrhosis – another complex disease in its own right – is superimposed on HCC. As a result, the prognostic range for these patients varies considerably and continues to change for each patient at every time point over the clinical course of their disease. A meta-analysis of 30 clinical trials into which HCC patients were enrolled for palliative treatment reflects this heterogeneity. It demonstrated a high variability in survival among untreated patients and concluded that no single patient characteristic alone could predict outcome [2].

The prognosis and treatment options for HCC are generally related to tumor stage and liver function at presentation [3,4]. In the west, approximately 30% of all patients with HCC are diagnosed in

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- adverse event management
- Child–Pugh B • dose modification • elderly
- hepatocellular carcinoma • mRECIST
- postprogression treatment
- real-world data • response assessment • sorafenib

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the early stages of the disease. For these patients, potentially curative treatment options, such as resection, transplantation and radiofrequency ablation, are available and offer a high probability of complete response. Approximately 20% of patients diagnosed with HCC have intermediate-stage disease and they can gain survival benefits of, on average, 20 months from treatment with transarterial chemoembolization (TACE), a locoregional treatment. However, for patients in the advanced stages of disease, who account for the majority of the HCC population, their disease is beyond resection and locoregional treatments are deemed ineffective. Consequently, the prognosis for advanced-stage HCC is poor [4].

Historically, the treatment options for advanced HCC were limited until the approval of sorafenib by the US FDA and the EMA in 2007. Sorafenib remains the only systemic therapy to date to have demonstrated a survival benefit in advanced HCC [5,6]. Since approval was granted to sorafenib, physicians have accrued a wealth of experience with the fine-tuning of sorafenib in their daily clinical practice, and several 'real-world' studies have continued to investigate the safety and efficacy of sorafenib. Among them is a multinational postmarketing study, GIDEON, and the Italian field-practice study by the Sorafenib Italian Assessment (SOFIA) study group [7–11], as well as a number of other studies in Europe and North America [12–15]. These real-world experiences have allowed us to assess sorafenib in patients who are not selected by strict clinical trial criteria but by physician judgment, including patients with comorbidities and those receiving concomitant medication.

Owing to the underlying liver disease, HCC is a notoriously difficult cancer to treat. This is reflected in the lack of agents that were approved before sorafenib and in the failure of recent clinical trials of other systemic therapies to meet their primary end points [4,16–19]. As sorafenib is currently the only approved systemic therapy that is available for HCC, it is important for physicians to know how best to use this agent in clinical practice in order to maximize the therapeutic benefits for their patients.

With this in mind, a panel of Italian experts convened in Italy in April 2013, at a meeting funded by Bayer Italy, in order to discuss which treatment strategies for sorafenib may facilitate the greatest patient benefit in clinical practice.

The key questions addressed during the expert meeting focused on the following areas:

- The dosing of sorafenib: in particular, the starting dose, the mean dose given in clinical studies and the use of dose modifications (including reductions and temporary interruptions);
- The evaluation of treatment response: specifically, how to evaluate progression, whether clinical or radiologic progression should be used, which evaluation criteria should theoretically and can practically be applied and how to weigh up the relative importance of tumor versus cirrhosis progression;
- Adherence to clinical guidelines in daily practice: specifically, the extent to and way in which guidelines are applied and the time point when treatment with a systemic agent should be initiated;
- The duration of treatment (DoT): in particular, when to stop sorafenib treatment and which treatment to use beyond progression, considering a rechallenge with sorafenib or switching to a second-line therapy;
- Communication with the patient: in particular, effective adverse event (AE) management and motivating the patient in order to extend patient adherence to sorafenib treatment.

In this article, we provide a synopsis of the main conclusions from the expert panel meeting in the anticipation that this will provide practicing physicians and other stakeholders with an understanding of how real-world experiences with sorafenib can help us to further refine and improve the management of patients with HCC.

The importance of starting right: sorafenib should be initiated at the approved dose

A Phase I pharmacokinetic study of sorafenib in patients with solid tumors identified 800 mg/day (administered as 400 mg twice daily) as the optimal dose to be tested in Phase II and III clinical trials of HCC [5–6,20–21]. This Phase I study was conducted in noncirrhotic patients. A subsequent Phase II trial using the same dose of sorafenib in cirrhotic Child–Pugh A and B patients with HCC detected no significant differences in the plasma pharmacokinetics of sorafenib between the two Child–Pugh groups

Table 1. Key outcomes from the SHARP[†] and Asia–Pacific[‡] randomized, placebo-controlled, Phase III trials of sorafenib in advanced hepatocellular carcinoma: selected baseline characteristics and efficacy data.

Characteristic/efficacy data	SHARP trial (n = 602)				Asia–Pacific trial (n = 226)			
	Sorafenib (n = 299)	Placebo (n = 303)	HR	p-value	Sorafenib (n = 150)	Placebo (n = 76)	HR	p-value
Baseline HCC stage								
BCLC stage C (%)	82	83	–	–	95	96	–	–
Baseline liver cirrhosis								
Child–Pugh A (%)	95	98	–	–	97	97	–	–
Child–Pugh B (%)	5	2	–	–	3	3	–	–
Response								
Complete (%)	0	0	–	–	0	0	–	–
Partial (%)	2	1	–	0.05	3	1	–	–
Stable disease (%)	71	67	–	0.17	54	28	–	–
Disease control rate (%)	43	32	–	0.002	35	16	–	0.0019
OS								
Median OS, months (95% CI)	10.7 (9.4–13.3)	7.9 (6.8–9.1)	0.69	<0.001	6.5 (5.56–7.56)	4.2 (3.75–5.46)	0.68	0.014
TTP								
Median radiologic TTP, months (95% CI)	5.5 (4.1–6.9)	2.8 (2.7–3.9)	0.58	<0.001	2.8 (2.63–3.58)	1.4 (1.35–1.55)	0.57	0.0005
Median symptomatic TTP, months (95% CI)	4.1 (3.5–4.8)	4.9 (4.2–6.3)	1.08	0.77	3.5 (2.80–4.24)	3.4 (2.40–4.08)	0.90	0.50

[†]Data taken from [6].

[‡]Data taken from [5].

BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; HR: Hazard ratio; OS: Overall survival; TTP: Time to progression.

(according to area under the curve, C_{\max} and t_{\max} values), confirming the tolerability of the 800-mg dose in cirrhotic patients [20].

The approval of sorafenib for the treatment of HCC at a dose of 800 mg/day was based on level I evidence from the SHARP trial, a randomized, Phase III trial in a western population [6], and was confirmed by another Phase III trial of similar design conducted in the Asia–Pacific region [5]. **Tables 1 & 2** summarize the main efficacy, safety and DoT data, as well as the rates of sorafenib dose modifications and discontinuations reported in these two trials. Since their publication, further support for initiating sorafenib treatment at the 800 mg/day dose has emerged from clinical practice and been captured by observational studies, such as GIDEON and SOFIA, which reported similar median survival outcomes and toxicity profiles that were analogous to the SHARP trial. **Tables 3 & 4** provide an overview of the study designs and key outcomes of these real-world studies.

Based on the strength of the trial data – sorafenib is supported by the highest level of evidence among treatments for HCC (**Figure 1**) – sorafenib 800 mg/day is the recommended standard of care for patients with advanced

HCC. It is also recommended for patients with intermediate HCC who are unsuitable for treatment with TACE or have TACE-refractory disease [4,24].

To our knowledge, no clinical trial in HCC has prospectively compared a different starting dose of sorafenib with the approved dose of 800 mg/day. The SOFIA study reported outcomes for patients who maintained an initial dose of 800 mg/day and for patients in whom the initial dose was reduced in order to manage AEs [9]. In a retrospective analysis, the authors reported a median overall survival (OS) of 21.6 months for patients who received 400 mg/day of sorafenib for 70% of the treatment period and 9.6 months for those who maintained full dosing or had a dose reduction for <70% of the treatment period. These results are affected by an inherent selection bias, as longer survival may be the cause, rather than the consequence, of dose reductions – the longer a patient receives active treatment, the greater the opportunity for AEs to develop, which in turn may require dose reductions. Furthermore, certain side effects, such as hand–foot skin reaction (HFSR), may be pharmacodynamic indicators of an individual's susceptibility to sorafenib, and may thus be associated with better outcomes, although the

Table 2. Safety, dose reduction, treatment discontinuation and duration of treatment outcomes for the SHARP and Asia-Pacific trials.[†]

Outcome	SHARP trial (n = 602)				Asia-Pacific trial (n = 226)			
	Sorafenib (n = 299)		Placebo (n = 303)		Sorafenib (n = 150)		Placebo (n = 76)	
Treatment-emergent AE[‡]								
All (%)	98		96		98		95	
Serious (%)	52		54		48		45	
Drug-related AE								
All (%)	80		52		82		39	
By severity grade[§]								
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
HFSR (%)	21	8	3	<1	45	11	3	0
Diarrhea (%)	39	8	11	2	26	6	5	0
Alopecia (%)	14	0	2	0	25	0	1	0
Fatigue (%)	22	4	16	<4	20	3	8	1
Rash/desquamation (%)	16	1	11	0	20	1	7	0
Hypertension (%)	5	2	2	1	19	2	1	0
Anorexia (%)	14	<1	3	1	13	0	3	0
Nausea (%)	11	<1	8	1	11	1	11	1
Dose reduction								
All (%)	26		7		31		3	
HFSR (%) [#]	5		–		11		0	
Diarrhea (%) [#]	8		–		7		0	
Discontinuation								
All (%)	38		37		20		13	
Hemorrhage, upper GI (%) [¶]	6		–		3		4	
Ascites (%) [¶]	–		–		3		3	
Fatigue (%) [¶]	5		–		3		0	
Liver dysfunction (%) [¶]	5		–		<1		3	
DoT								
Median DoT, months (range)	5.3 (0.2–16.1)		4.3 (0.1–16.6)		–		–	

[†]Data taken from [5,6].
[‡]AE occurring in at least 5% of patients.
[§]According to CTCAE v3.0.
[#]Most frequent reasons for dose reduction.
[¶]Most frequent reasons for treatment discontinuation.
 AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DoT: Duration of treatment; GI: Gastrointestinal; HCC: Hepatocellular carcinoma; HFSR: Hand-foot skin reaction.

underlying mechanisms are not yet understood [25–27]. Thus, the patients in the reduced-dose group may be the patients who most readily respond to the Raf-inhibitory (therapeutic) effects of sorafenib [25,27]. At the same time, on the same dose, patients in whom the pharmacokinetics of sorafenib are shifted towards the lower end of susceptibility or who have a more aggressive form of HCC will have a worse outcome. Hypothetically, in these patients, the paradoxical growth-enhancing effect of sorafenib at lower doses (reported in a rodent model) may also come into play [28,29].

In this context, it is insightful to consider a pharmacokinetic study of sorafenib by Miller

and colleagues in solid-cancer patients with hepatic or renal dysfunction [30]. Despite corroborating the results of another trial by failing to show a significant difference in the pharmacokinetics of a 400-mg dose of sorafenib between Child–Pugh A and B patients [31], the authors did find that higher bilirubin concentrations were associated with lower areas under the curve of the main sorafenib metabolite, *N*-oxide-sorafenib, but only in the hepatic and not the renal cohort. Sorafenib was also only found to be associated with a dose-limiting elevation of bilirubin in patients with hepatic but not renal dysfunction. Miller *et al.* speculate that this intolerance may be linked to the inhibition of

Table 3. Overview of the study design and outcomes from the GIDEON and SOFIA real-world studies of sorafenib in HCC[†]: study design and efficacy/effectiveness outcomes.

Design/outcome	GIDEON trial (n = 3202)	SOFIA trial (n = 296)
Study design	Global, prospective, noninterventional study of patients with unresectable HCC eligible for systemic therapy and treated with sorafenib under real-life practice conditions in order to evaluate the safety and efficacy of sorafenib in different subgroups. The recruitment aim was 3000 patients from >40 countries, with a follow-up of approximately 5 years	Italian, six-center, investigator-driven, observational, noninterventional study in order to assess the safety and effectiveness of sorafenib in patients with advanced HCC or intermediate HCC not eligible for or having failed ablative therapies. Consecutive evaluation of patients took place between 2008 and 2012
Baseline HCC stage		
BCLC stage B (%)	20	25
BCLC stage C (%)	52	75
Baseline liver cirrhosis		
Child–Pugh A (%)	62	88
Child–Pugh B (%)	21	37
Median OS		
Total (months)	–	10.5
Child–Pugh A (months)	13.6	–
Child–Pugh B (months)	5.2	–
BCLC stage B (months)	–	20.6
BCLC stage C (months)	–	8.4
Median radiologic TTP		
Overall (months)	–	9.2
Child–Pugh A (months)	4.7	–
Child–Pugh B (months)	4.4	–

[†]Data taken from [5,6,9–11,31,32].
BCLC: Barcelona Clinic Liver Cancer; HCC: Hepatocellular carcinoma; OS: Overall survival; TTP: Time to progression.

uridine diphosphate-glucuronosyl-transferase by sorafenib.

Even in the real-world SOFIA study, the sorafenib starting dose was 800 mg/day and was reduced only as required by intolerance or AEs. Dose adjustments for the purpose of managing AEs are a valid strategy for avoiding permanent discontinuation where possible and thus ensuring that no treatment benefit is lost.

Real-world noninterventional studies, such as GIDEON, have so far not delivered evidence to suggest that a lower starting dose of sorafenib may improve or at least result in equal clinical effectiveness compared with the recommended starting dose of 800 mg/day [25,32]. Data from GIDEON showed that patients on the higher, approved, 800-mg starting dose had better efficacy outcomes than patients starting treatment on a dose of 400 mg/day [11,22]. In this real-world study, 74% of patients started sorafenib treatment at the approved dose. In terms of HCC disease stage, liver function and prior surgery or locoregional treatment, these patients were similar to the 22% of patients given the 400 mg/day starting dose. On average, patients

who started treatment at 800 mg/day remained on treatment for 2.6 weeks longer than patients starting on 400 mg/day. In these patients, median OS was extended by over 2 months and median time to progression (TTP) was extended by approximately 1 month compared with the lower-starting-dose group (9.3 vs 7.1 months and 4.5 vs 3.6 months, respectively) [22]. In terms of safety, the findings for the approved- and low-dose groups were similar, with approximately 30% of patients receiving sorafenib dose modifications irrespective of the starting dose (35% with 800 mg/day and 32% with 400 mg/day) and no significant differences in the types or incidences of AEs between the two groups [11,22]. A recent subanalysis of European patients included in the GIDEON noninterventional study has closely echoed these findings [23].

To stop or not to stop sorafenib? When is the question

The median DoT with sorafenib was 5.3 months in the Phase III SHARP trial and 3.8 and 3.4 months in the real-world SOFIA and GIDEON studies, respectively [6,9–10], suggesting that

sorafenib may be stopped prematurely in some clinical scenarios. It is crucial to understand the key drivers behind why this may happen. Two possible explanations include discontinuation because of sorafenib-associated or disease-related AEs and/or a perceived absence of tumor response and clinical benefit with sorafenib.

• **How AEs may influence treatment decisions with sorafenib**

Understanding how to optimize the use of sorafenib in daily clinical practice – including how to modify the dose appropriately according to the type and severity of AEs and how to effectively manage sorafenib-associated AEs – is important

Table 4. Safety, dose reduction, treatment discontinuation and duration of treatment outcomes for the GIDEON and SOFIA trials.

Outcome	GIDEON trial (n = 3202)		SOFIA trial (n = 296)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-emergent AE[†]				
Overall (%)	85	30	91	45
Serious AE (%)	43	–	–	–
Drug-related AE	Any grade	Grade 3/4	Any grade	Grade 3/4
Overall (%)	66	23	–	–
Drug-related serious AE (%)	9	–	–	–
HFSR (%)	27	–	28	9
Diarrhea (%)	27	–	35	6
Alopecia (%)	7	–	–	–
Fatigue (%)	16	–	66	25
Rash/desquamation (%)	11	–	5	2
Hypertension (%)	9	–	18	7
Anorexia (%)	10	–	–	–
Nausea (%)	7	–	11	3
Weight loss (%)	–	–	39	6
Constipation (%)	–	–	16	0
Stomatitis (%)	–	–	6	0
GI bleeding (%)	–	–	9	5
Any cardiovascular event (%)	–	–	5	2
Dose reduction				
Overall (%)	33 [‡]		54	
Any AE (%) [§]	–		83	
Deteriorated liver function (%) [§]	–		9	
Fatigue (%) [§]	–		21	
HFSR (%) [§]	–		10	
Diarrhea (%) [§]	–		8	
Discontinuation				
Overall (%)	–		79	
Any AE (%) [#]	31		32	
Fatigue (%) [#]	–		7	
Deteriorated liver function (%) [#]	–		13	
HCC progression (%) [#]	–		34	
Median DoT				
Overall (months)	3.5		3.8	
If interrupted due to AE (months)	–		1.7	
If interrupted due to progression (months)	–		8.7	

[†]AE occurring in at least 5% of patients.

[‡]2nd interim analysis, N = 1571.

[§]Most frequent reasons for dose reduction.

[#]Most frequent reasons for treatment discontinuation.

AE: Adverse event; DoT: Duration of treatment; HCC: Hepatocellular carcinoma; HFSR: Hand-foot skin reaction; NOS: Not otherwise specified.

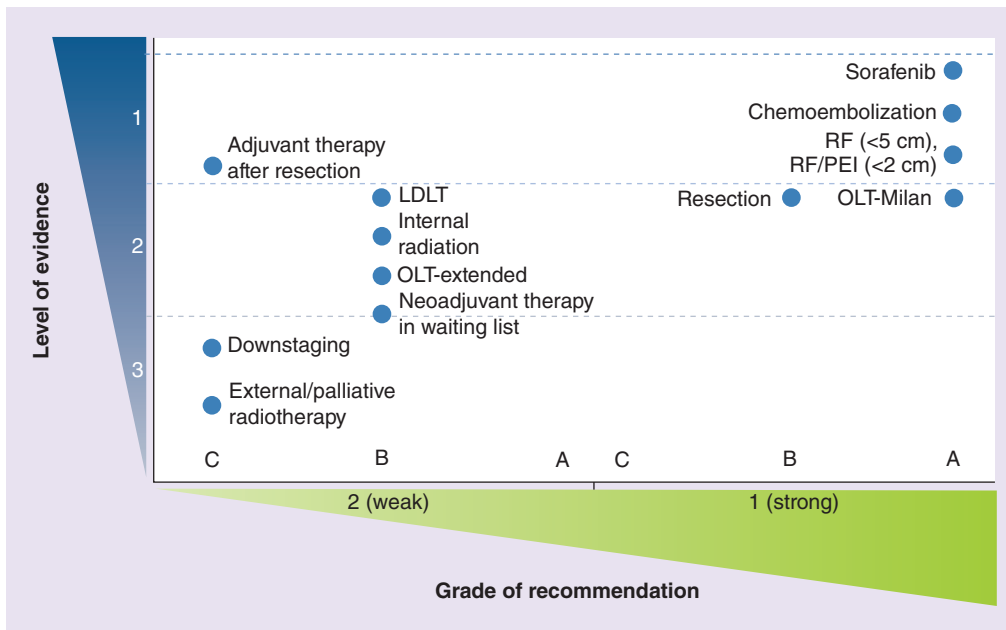


Figure 1. Sorafenib is associated with the highest level of evidence in the European Association for the Study of the Liver–European Organisation for Research and Treatment of Cancer guidelines for the management of hepatocellular carcinoma.

LDLT: Living-donor liver transplantation; OLT: Orthotopic liver transplantation; PEI: Percutaneous ethanol injection; RF: Radiofrequency ablation.

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in order to achieve the longest possible DoT, and with this, the best possible patient benefit.

Sorafenib dose modification during therapy is a viable treatment strategy for maximizing patient outcomes

Real-world studies of patients with HCC have confirmed that sorafenib has an AE profile that is consistent with the those observed in Phase III clinical trials, offering reassurance that the management strategies already developed in the clinical trial setting remain applicable in the real-world setting [5–6,9–11,22–23]. In advanced HCC, AEs due to sorafenib treatment occur mainly during the first month of treatment and progressively reduce in frequency thereafter [13]. It is therefore imperative that patients should be monitored closely, especially during the first weeks of therapy.

As observations from the SOFIA study have shown, if patients with sorafenib-associated AEs are managed appropriately by adopting appropriate dose modification or treatment interruption strategies promptly, they can be maintained on treatment for longer, resulting in improved clinical outcomes [9]. All patients in the SOFIA study were started on the recommended full dose of

sorafenib: 800 mg/day. In the event of clinically relevant grade 3 or 4 AEs, the sorafenib dose was reduced to 400 mg/day or a temporary dose interruption was introduced until symptoms resolved to grade 1 or 2 severity, in accordance with the sorafenib label. Re-escalation to the full dose was performed when possible. Deterioration of hepatic function due to the underlying liver disease was another criterion for dose modification or interruption. Revealingly, the median DoT in the 26% patients who had undergone dose modification in order to manage AEs for more than 70% of the time was longer (6.8 months) than in patients who had been maintained on the recommended dose (800 mg/day) for more than 70% of the time (3 months); the patients with dose modifications had a median OS of 21.6 months. Thus, in patients with longer survival times, dose reductions were frequently reported, suggesting that these reductions do not abolish the beneficial effects of sorafenib (see [Table 4](#) for an overview of the dose reduction and discontinuation findings of the SOFIA study).

In addition, reports of individual case studies have highlighted the importance of prolonged sorafenib administration, even at a reduced dose. Abbadessa and colleagues observed two partial

Table 5. Summary of dose modifications for skin toxicity.

Skin toxicity grade	Occurrence	Suggested dose modification
Grade 1: numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet that does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief
Grade 2: painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	First occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below
	No improvement within 7 days or second or third occurrence	Interrupt sorafenib treatment until toxicity resolves to grade 0–1. When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day)
	Fourth occurrence	Discontinue sorafenib treatment
Grade 3: moist desquamation, ulceration, blistering or severe pain of the hands or feet or severe discomfort that causes the patient to be unable to work or perform activities of daily living	First or second occurrence	Interrupt sorafenib treatment until toxicity resolves to grade 0–1. When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day)
	Third occurrence	Discontinue sorafenib treatment

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Table 6. Summary of the Response Evaluation Criteria In Solid Tumors and the modified Response Evaluation Criteria In Solid Tumors.

RECIST	mRECIST
CR: disappearance of all target lesions	CR: disappearance of any intratumoral enhancement in all target lesions
PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR: at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD: any cases that do not qualify for either PR or PD	SD: any cases that do not qualify for either PR or PD
PD: an increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

CR: Complete response; mRECIST: Modified response evaluation criteria in solid tumors; PD: Progressive disease; PR: Partial response; RECIST: Response evaluation criteria in solid tumors SD: Stable disease.

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and two complete responses, with progression-free survival ranging from 12 to 62 months, after maintaining four patients on sorafenib for over 12 months (in one case even 30 months) through the carefully judged use of dose-modification strategies [33]. At this juncture, it is appropriate to highlight that the DoT in the clinical practice setting may be inherently shorter in some patients in which the 800 mg/day dose is not reduced (e.g., if sorafenib is stopped earlier in patients with a more aggressive disease [and therefore with a poorer prognosis] or when the pharmacokinetics variability of sorafenib results in reduced exposure and possible decreased efficacy in some individuals).

An example of how sorafenib dose modifications can be implemented effectively in clinical practice is illustrated by the guidance for HFSR management (Table 5) [3]. Whether triggered by HFSR or another AE, the dose-modification strategy should take into consideration

the re-escalation of sorafenib, after sufficient improvement of the AE. This step will ensure that the clinical benefit associated with sorafenib treatment is maximized.

In patients who tolerate the treatment less well, sorafenib dose modification should always be considered first before permanent discontinuation

Certain patient groups naturally elicit a more conservative approach when it comes to dosing with sorafenib [25]. One such group comprises the Child–Pugh B population, which has been reported to fare worse than Child–Pugh A patients. In the SOFIA study, Iavarone *et al.* observed the deterioration of hepatic function in a greater proportion of Child–Pugh B (40%) than Child–Pugh A patients (16%) after 24 weeks of sorafenib treatment [9]. The GIDEON study reported that the incidence of drug-related AEs was generally consistent across Child–Pugh

A and B subgroups, although serious AEs were more common in Child–Pugh B patients. This study also showed that discontinuation of treatment due to AEs in the real-world setting was more common in Child–Pugh B patients (40.1 vs 28.9%) [5–6,9–11,22–23].

Elderly patients make up another group. A recent review of this population in HCC trials (in which they are usually chronically under-represented) suggests that the elderly are treated more conservatively compared with younger patients at the same stage of disease, but concludes that age cannot be defined a contraindication to therapy at present because it does not adversely affect outcome, although it may condition treatment allocation [34]. However, until the availability of data from pharmacokinetic/pharmacodynamic analyses of individual patients with different clinical characteristics, which may allow for a more personalized therapy approach (e.g., tailored to severe comorbidities or impaired performance status), expert opinion clearly recommends that early dose modifications should be explored in patients who are intolerant of the full dose of sorafenib before a decision is taken to suspend treatment entirely [32].

There is a broad range of treatment strategies available to effectively manage or prevent AEs with sorafenib

Advising patients on preventive strategies, emphasizing the importance of early detection and explaining the clinical relevance of AEs all play a crucial role in avoiding the premature discontinuation of sorafenib. To this end, a wide variety of recommendations have been developed by multidisciplinary teams and are available in order to guide physicians in their management of the most common AEs associated with sorafenib [35–41]. Recommendations for managing HFSR, diarrhea, fatigue, and hypertension are shown in **Table 6** and **Boxes 1–4**.

Response criteria for targeted therapies: ensuring sorafenib is maintained in order to maximize clinical outcomes

There is much debate as to which criteria should be used in order to assess tumor response to targeted therapies, such as sorafenib [47]. The appropriate assessment of tumor response is critical for ensuring that treatment is not discontinued prematurely because of a perceived absence of clinical benefit.

Traditional Response Evaluation Criteria In Solid Tumors may not be appropriate for measuring response to sorafenib

Treatment response to cytotoxic agents has typically been evaluated with the Response Evaluation Criteria In Solid Tumors (RECIST) [48]. However, after the advent of targeted cancer therapies, RECIST was found to be suboptimal because of its restriction to tumor shrinkage as the sole measure of response. As a consequence, RECIST may not accurately reflect responses to treatments that cause tumor necrosis without an initial shrinkage of the tumor dimensions, as occurs with locoregional therapies [47,48]. This has raised the question of whether physicians are stopping treatment with targeted therapies, including sorafenib, too soon as a consequence of not being able to detect or evaluate tumor response reliably. The modified RECIST (mRECIST) criteria were developed in order to accommodate the requirement for both tumor necrosis and viability assessment (**Table 6**) [42,47] and are recommended by current treatment guidelines for evaluating tumor response in patients with HCC [4,24]. However, although preliminary retrospective evidence supports the use of mRECIST in HCC in order to assess tumor response to sorafenib, additional validation in larger studies is required [25,49–50].

Sorafenib should not be discontinued based on radiologic response alone

By relying on radiologic response alone, physicians may be stopping sorafenib too early. It is important to note that both of the Phase III trials of sorafenib in advanced HCC, on the basis of which this treatment was approved, stipulated that sorafenib was to be continued until the occurrence of both radiologic (at that time using RECIST prior to the definition of mRECIST) and symptomatic progression [5–6,9]. Indeed, one of the defined primary outcomes in these trials was time to symptomatic progression using the Functional Assessment of Cancer Therapy – Hepatobiliary Symptom Index 8 (FHSI8) questionnaire in order to assess symptomatic progression [5,6]. The approach of using nonradiologic progression as an indicator of when to cease sorafenib treatment was also adopted by the SOFIA group in their field practice study, in which treatment was continued until either radiologic or symptomatic progression [9]. In order to extend OS and improve quality of life for the patient, it is thus paramount that other clinical

Box 1. Recommendations for the management of rash and hand–foot skin reaction with sorafenib treatment.

- Inform patients of the full range of rash and HFSR symptoms so that they know what to expect.
- Advise patients that prompt reporting and treatment of mild HFSR may prevent HFSR progression and allow continued full-dose therapy. Advise patient to keep good daily hygiene procedures.
- Treat any pre-existing dermatologic conditions.
- Specific recommendations for HFSR:
 - Application of keratolytic creams (containing urea, α -hydroxy acids or salicylic acid) in order to aid natural exfoliation; emollient creams for moisturization; appropriate use of topical corticosteroids; and topical analgesics.
- Specific recommendations for rash:
 - Management with over-the-counter body lotions containing exfoliative α -hydroxy acid components, zinc oxide-based emollients, lanolin-based creams and antihistamines.
- Dose adjustment to be used for severe cases of rash and HFSR, with re-escalation to full sorafenib dose if tolerated once AEs have resolved.

Rash and HFSR are among the most common dermatologic AEs associated with sorafenib.

AE: Adverse event; HFSR: Hand–foot skin reaction.

Recommendations are supported by [3,35–38,41,60–61].

factors and read-outs of oncologic effect are considered alongside radiologic response. According to clinical judgment, treatment with sorafenib should be maintained in patients who continue to demonstrate a clinical benefit from therapy (i.e., a stable clinical condition).

Identifying markers of tumor response may help to guide sorafenib therapy & predict prognosis

The identification of biological markers is an exciting area of current translational research and holds the possibility of eventually tailoring treatment and/or dosing to best effect in individual patients. One objective of the SHARP trial was to explore the ability of plasma biomarkers to predict patient prognoses and sorafenib efficacy. The authors of the SHARP biomarker analysis reported that baseline angiopoietin 2, VEGF concentrations, α -fetoprotein and alkaline phosphatase

concentrations, as well as macroscopic vascular invasion and Eastern Cooperative Oncology Group (ECOG) status, independently predicted survival in the patient population as a whole, and that high s-c-KIT or low HGF concentrations at baseline were associated with a trend in favor of improved survival in patients treated with sorafenib [51]. However, no biomarker has yet been validated for selecting patients for sorafenib therapy.

Other recent studies have investigated plasma biomarkers as potential markers of response to sorafenib (and other antiangiogenic therapies), such as α -fetoprotein [52–55], and additional research is ongoing. There are also some small studies that suggest that sorafenib AEs (e.g., skin toxicity and hypertension) may be markers of clinical efficacy and that the pattern of disease progression on sorafenib treatment may predict the postprogression prognosis [27,56]. This information may be useful in the design of second-line

Box 2. Recommendations for the management of diarrhea with sorafenib treatment.

- Encourage patients to use a stool diary, report any abnormalities or deterioration in symptoms and seek medical advice if concerned.
- Discuss dietary measures with the patient:
 - Avoid high-fiber foods or those that aggravate diarrhea.
- Implement dehydration prevention management:
 - For example, by aggressive oral rehydration with electrolytes.
- Consider pharmacologic management (e.g., loperamide):
 - Loperamide schedule recommended by a European nurse task group [38]:
 - 4 mg followed by 2 mg every 2 h until 2 h after the last bowel movement.
 - For patients with long-term diarrhea, 2–4 mg twice daily titrated according to bowel function.
 - A preventative measure in order to avoid recurrent diarrhea is to take loperamide 30 min prior to sorafenib treatment.
- Dose adjustment to be used as necessary for grade 3–4 diarrhea (dose reduction and/or interruption), with re-escalation to full sorafenib dose if tolerated once the AE has resolved.

Management of diarrhea should be carried out by a hepatologist, who can adequately consider complications potentially arising in cirrhotic patients.

AE: Adverse event.

Recommendations are supported by [38,41,60,62].

Box 3. Recommendations for the management of fatigue with sorafenib treatment.

- Advise the patient to self-monitor fatigue levels and adopt energy-conserving strategies when needed
- Consider nonpharmacological interventions:
 - Activity enhancement (e.g., exercise as appropriate).
 - Cognitive behavioral therapy.
 - Nutrition consultation.
- Consider pharmacological interventions:
 - Psychostimulants.
 - Treatment for pain, emotional distress, anemia and hypothyroidism.
 - Treatment for sleep dysfunction, nutritional imbalances/disturbances and comorbidities.
- Dose adjustment
 - Grade 3–4 fatigue requires treatment interruption or dose adjustment, with re-escalation to full sorafenib dose if tolerated once the AE has resolved.

Fatigue is an underlying symptom of cancer and other comorbidities. Investigation of the possible reasons for fatigue is important in order to implement the appropriate management.

AE: Adverse event.

Recommendations are supported by [3,40,60,63].

studies as well as in clinical decision-making for the postprogression continuation of sorafenib. However, data from large, prospective studies are required in order to confirm this hypothesis.

Finally, it has been shown that the pattern of tumor progression that is observed during sorafenib treatment may impact on survival and could potentially be used in order to determine patient prognosis [12]. For example, the appearance of new extrahepatic lesions is associated with worse postprogression survival than progression without new extrahepatic lesions (7.1 vs 14.9 months, respectively; $p = 0.02$).

Using sorafenib in Child–Pugh B patients

Child–Pugh B patients are of special interest in terms of sorafenib management, as the progression of their cirrhosis, rather than tumor progression,

may result in the discontinuation of sorafenib. As a whole, the data available on the safety of sorafenib in Child–Pugh B patients suggest the feasibility of using this treatment in this population, taking into account the fact that poorer clinical outcomes are to be expected due to worse liver function [3]. However, more robust studies are necessary before confirming or disregarding the use of sorafenib in this subset of patients [3]. The ongoing BOOST Phase III study is aiming to address this question. This study will compare OS with sorafenib (800 mg/day) versus best supportive care in 320 patients with HCC and impaired liver function (Child–Pugh B; NCT01405573). In addition, the ongoing PRODIGE 21 Phase II randomized trial will evaluate time to radiologic progression in 160 patients with HCC and Child–Pugh B cirrhosis receiving sorafenib alone, pravastatin alone

Box 4. Recommendations for the management of hypertension with sorafenib treatment.

- Monitor blood pressure regularly:
 - Once a week for the first 6 weeks of sorafenib treatment.
 - Continue weekly monitoring in patients with pre-existing hypertension.
- Pre-existing hypertension:
 - Mild-to-moderate increases in blood pressure can be managed by increasing the dose of the patient's current antihypertensive medication or adding a new antihypertensive medication.
- New-onset hypertension:
 - This can be effectively managed with standard antihypertensive therapy (appropriate to the individual patient and clinical situation), which includes angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors, according to standard practice guidelines (e.g., European Society of Cardiology/European Society of Hypertension guidelines)
- Dose adjustment
 - Dose reductions/interruptions can be used in order to manage hypertension if required, and in cases of severe or persistent hypertension that do not respond to antihypertensive drug treatment, permanent discontinuation of sorafenib should be considered

In patients receiving sorafenib, hypertension is usually mild to moderate, occurs early in therapy and can often be managed with standard antihypertensive therapy.

AE: Adverse event.

Recommendations are supported by [60,62].

or the combination of sorafenib and pravastatin (NCT01357486).

In the GIDEON study, 61.5% of patients were classified as having Child–Pugh A status and 20.8% as having Child–Pugh B status [10]. Overall, this noninterventional study showed that a greater proportion of Child–Pugh B than Child–Pugh A patients discontinued sorafenib because of AEs (40.1 vs 28.9%) or experienced grade 3/4 AEs (14.1 vs 8.8%). Nevertheless, just over a quarter of patients with Child–Pugh B cirrhosis (25.7%) were treated with sorafenib for over 24 weeks and the TTP was comparable between the Child–Pugh A and B cohorts (4.7 vs 4.4 months, respectively); however, not surprisingly, median survival in the Child–Pugh B cohort was shorter by approximately 8 months (13.6 vs 5.2 months; **Table 3**).

Similar findings were also observed in a multicenter, open-label, Phase II trial of sorafenib (800 mg/day) performed in 297 patients with Child–Pugh A (79%) and Child–Pugh B (21%) liver function [14]. Compared with their Child–Pugh A counterparts, patients with Child–Pugh B status had shorter progression-free survival (PFS; 2.1 vs 4.3 months), moderately shorter TTP (3.8 vs 4.2 months) and clearly reduced OS (3.8 vs 10.0 months). Again, the overall AE profile was similar in the two groups.

The results of these studies are not surprising, given that patients with Child–Pugh B liver function have a poorer prognosis as a consequence of their more advanced liver cirrhosis, justifying the development of sorafenib in the SHARP study in a Child–Pugh A population of patients. Indeed, a subgroup analysis from the GIDEON study that stratified patients with Child–Pugh B status according to individual scores (B7, B8 and B9) showed that median OS shortened as the Child–Pugh B score increased in severity [10].

Using sorafenib in the elderly

Trials of sorafenib in elderly patients are scarce, and to our knowledge, only three studies – all cohort studies – have evaluated treatment with sorafenib in this patient population. The efficacy results varied among these studies, with reported median survival values ranging from 5.3 to 16 months. With regards to safety profiles, certain AEs were observed more frequently, as may be expected in an elderly population that is inherently more likely than younger patients to have comorbidities that may affect tolerability.

In the only prospective cohort study, Di Costanzo and colleagues compared treatment with sorafenib at 800 mg/day in 90 younger patients (age <70 years) and 60 older patients (age >70 years) with compensated cirrhosis and advanced HCC or HCC that was not eligible for locoregional therapies [57]. Both TTP and OS were shorter in the younger group compared with the older patients (8 vs 12 months and 12 vs 16 months, respectively). Although the general safety profile was similar, grade 3 and 4 AEs were observed more frequently in the younger than the older group (15.7 vs 9.2%).

Of the two other retrospective trials, only one was comparative. It included 172 consecutive patients with advanced HCC and compensated cirrhosis treated with sorafenib and reported that OS (5.32 vs 5.16 months) and AEs related to sorafenib were comparable in a cohort of 35 elderly patients (≥ 70 years) and one of 135 younger patients (<70 years). Unsurprisingly, the older patients more frequently experienced comorbid cardiovascular conditions, but were also found to suffer grade 3 or 4 malaise, mucositis and neutropenia significantly more frequently than the younger cohort [58].

In a single-arm study, 60 elderly patients (>70 years) with advanced HCC were started on a low dose of sorafenib (400 mg/day) that was scaled up to 600 mg/day after 2 weeks and then 800 mg/day after another 2 weeks, providing no AEs or impairment of residual liver function occurred. Ultimately, 18.3% of these patients were able to reach the full daily dose of sorafenib. The median OS in this study was 10.0 months [59].

Finally, the results of a multivariate analysis from the SOFIA field study showed that age was not significantly associated with mortality, but it was independently related to discontinuation of therapy due to intolerance [9].

Treatment beyond progression

For patients who experience progression during sorafenib treatment, further treatment options are limited. According to a consensus statement of European HCC specialists, the first option for these patients is inclusion in second-line clinical trials where available [60].

Should alternative therapies with proven efficacy in the second-line setting not be available, the consensus statement recommends the continuation of sorafenib treatment after disease progression, which may be beneficial in slowing down tumor growth [60–62]. Evidence

supporting this approach has recently come from a study measuring the size of metastatic lesions in patients with advanced HCC following their first radiologic progression of disease while receiving sorafenib [62]. The patients were divided into those either continuing to receive sorafenib (n = 23) or those stopping treatment (n = 13). There was no increase in the growth rate of lesions after progression in patients who continued sorafenib treatment, while the growth rate was seen to increase in those patients who had stopped sorafenib after progression (p = 0.002). Survival beyond first progression was also longer in the postprogression sorafenib continuers (median: 11.9 months) than in the discontinuers (median: 5.2 months; p = 0.012) [62]. However, as the postprogression survival of patients continuing sorafenib exceeded the median OS of all patients in the SHARP trial, as well as most other sorafenib studies in HCC, this study may be subject to selection bias that limits the ability to interpret the results.

In a study by Rimassa *et al.*, the strategy of sorafenib dose escalation upon disease progression while on sorafenib failed to demonstrate any improvement in clinical outcome [63]. This prospective study did not meet its primary end point of improved PFS in patients who were escalated to sorafenib 1200 mg/day (n = 49) compared with those who received best supportive care (n = 52) following radiologic disease progression while on sorafenib 800 mg/day; the PFS values were 3.91 vs 2.69 months, respectively (p = 0.086).

Expert opinion thus concludes that sorafenib may be continued after disease progression for patients with stable performance status, although there is currently no clear evidence from large studies supporting the effectiveness of this approach [60,61].

Conclusion

HCC is extremely heterogeneous in its nature and in most cases develops on a background of liver cirrhosis that has its own natural history. Therefore, demonstration of effectiveness of therapies in this disease is a complex and difficult task. To date, sorafenib is the only available systemic therapy for patients with more advanced stages of HCC and as such needs to be used effectively in daily clinical practice in order to maximize patient outcomes. For one, such effective use can be achieved by a clear understanding of how to manage AEs through sorafenib dose modification and effective prophylactic

measures, which are critical for maintaining patient adherence and thus extending treatment duration. Furthermore, employing the appropriate criteria for assessing tumor responses to sorafenib in order to prevent premature treatment discontinuation is also enormously important.

While there are currently no reliable biomarkers of response for guiding treatment decisions with sorafenib, this represents an important area of ongoing research that will help to further refine our lessons with this valuable agent in the future. The data available for sorafenib in Child–Pugh B patients suggest the potential feasibility of this treatment in this population. However, more robust studies are necessary before confirming the use of sorafenib in this subset of patients and results from ongoing studies are eagerly awaited. For the elderly population of patients with HCC, treatment with sorafenib is feasible, although their potentially higher comorbidity status needs to be taken into consideration.

There are currently no approved second-line options for patients who progress on sorafenib. Patients should be recruited into second-line trials where available. Sorafenib may be continued after disease progression, but additional data are required in order to confirm the effectiveness of this approach.

Future perspective

Sorafenib will continue to be a valuable first-line treatment option for patients with advanced HCC or intermediate-stage patients who are unsuitable for or refractory to treatment with TACE. The use of sorafenib will be further optimized in the future through continued physician and patient education, and eventually by reliable biomarker analyses coming online. Despite recent clinical trials in the first- and second-line setting that have failed to reach their clinical end points, we must have hope that new systemic agents will be approved in the future in order to further improve clinical outcomes in patients with HCC. Once this is realized, the question of the appropriate use of sorafenib in relation to other treatments, be it in sequence or in combination, will undoubtedly be the subject of much debate and clinical investigation.

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EXECUTIVE SUMMARY

The importance of starting right: sorafenib should be initiated at the approved dose

- Sorafenib is the only available systemic therapy that is recommended for patients with advanced hepatocellular carcinoma and those who are not suitable for transarterial chemoembolization or have transarterial chemoembolization-refractory disease. Treatment with sorafenib should be initiated at the recommended dose of 800 mg/day as there is no evidence to suggest that starting at a lower dose ensures the same clinical outcomes or improves tolerability. In particularly fragile patients (e.g., Child–Pugh B status, elderly and/or clinically significant cardiovascular comorbidity), a 1-month ramp-up strategy may be acceptable in order to test individual tolerability.

To stop or not to stop sorafenib? When is the question

- Having a clear understanding of how to manage adverse events (AEs) through sorafenib dose modification and effective prophylactic measures is critical for maintaining patient adherence and extending treatment duration. Rather than discontinuing sorafenib too early at the appearance of the first AE, sorafenib should be continued through dose modification and effective AE management strategies in order to maximize patient outcomes.
- Using the appropriate criteria for assessing tumor responses to sorafenib is also important for preventing premature discontinuation. The modified Response Evaluation Criteria In Solid Tumors more accurately measures tumor responses compared with the Response Evaluation Criteria In Solid Tumors. Preliminary data suggest that the modified Response Evaluation Criteria In Solid Tumors could be used in order to assess response to sorafenib, but confirmation in larger, prospective studies is required.
- Sorafenib should not be discontinued on radiologic response alone, but patients should also be assessed for other outcomes, such as symptomatic progression, in order to extend overall survival and quality of life.
- While there are currently no reliable biomarkers of response for guiding treatment decisions with sorafenib, this represents an important area of ongoing research that will help to further refine our lessons with this valuable agent in the future.

Using sorafenib in Child–Pugh B patients

- Data available for sorafenib in Child–Pugh B patients suggest the potential feasibility of this treatment in this population. However, more robust studies are necessary before confirming the use of sorafenib in this subset of patients, and results from ongoing studies are awaited.

Using sorafenib in the elderly

- The data available for sorafenib in elderly patients suggest the potential feasibility of this treatment in this population, bearing in mind that comorbidities are likely to be more frequent.

Treatment beyond progression

- There are currently no approved second-line options for patients who progress on sorafenib. Patients should be recruited into second-line trials where available. Sorafenib may be continued after disease progression, but additional data are required in order to confirm the effectiveness of this approach.

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