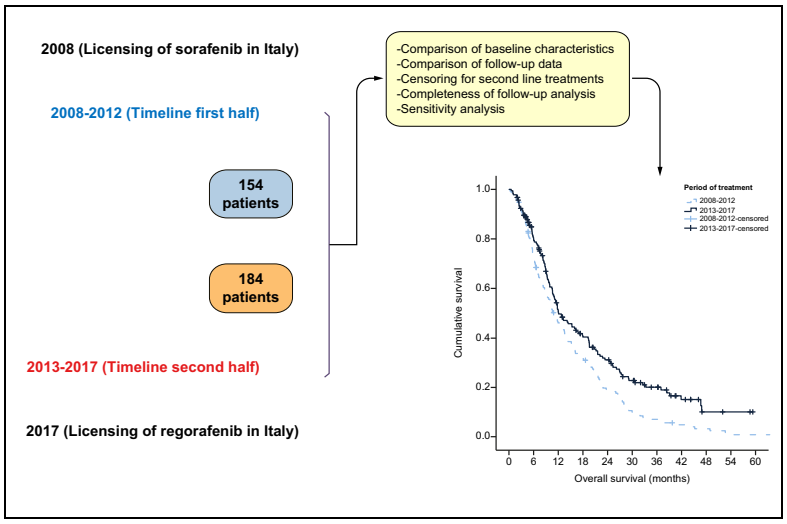
Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Management of adverse events with tailored sorafenib dosing prolongs survival of hepatocellular carcinoma patients

Graphical abstract



Highlights

- Management of sorafenib-related adverse events has changed over time.
- A tailored approach with more temporary dose reductions is now more frequent.
- Median treatment duration has increased overtime (5.8 *vs.* 4.1months).
- More importantly, overall survival has also increased (12.0 *vs.* 11.0months).
- Increasing survival impacts on the design of trials using sorafenib as comparator.

Authors

Francesco Tovoli, Luca Ielasi, Andrea Casadei-Gardini, ..., Giulia Orsi, Matteo Renzulli, Fabio Piscaglia

Correspondence

francesco.tovoli2@unibo.it
(F. Tovoli)

Lay summary

Sorafenib has been the standard frontline systemic treatment for hepatocellular carcinoma for over a decade. Its tolerability is limited by different adverse events, which might lead to its permanent discontinuation in a sizeable proportion of patients. After a careful analysis of potential confounders, we demonstrated that the physicians experience in managing adverse events related to sorafenib has improved over time, with longer treatment periods and less permanent discontinuation for toxicities. More importantly, these improvements also translated into longer patient survival. Our results have relevant repercussions in clinical practice and in the design of future clinical trials.

http://dx.doi.org/10.1016/j.jhep.2019.08.015

Research Article

JOURNAL OF HEPATOLOGY

Management of adverse events with tailored sorafenib dosing prolongs survival of hepatocellular carcinoma patients

Francesco Tovoli[1,*], Luca Ielasi[1], Andrea Casadei-Gardini[2,3], Alessandro Granito[1], Francesco Giuseppe Foschi[4], Giulia Rovesti[3], Giulia Negrini[1], Giulia Orsi[3], Matteo Renzulli[5], Fabio Piscaglia[1]

[1]*Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy;* [2]*Department of Medical Oncology, Istituto Scientifico Romagnolo per Lo Studio e Cura Dei Tumori, Meldola, Italy;* [3]*Department of Oncology and Haematology, University Hospital of Modena, Modena, Italy;* [4]*Department of Internal Medicine, Degli Infermi Hospital, Faenza, Italy;* [5]*Unit of Radiology, Department of Diagnostic Medicine and Prevention, Sant'Orsola Hospital, University of Bologna, Bologna, Italy*

Background & Aims: Sorafenib is associated with multiple adverse events (AEs), potentially causing its permanent interruption. It is unknown how physicians' experience has impacted on the management of these AEs and consequently on clinical outcomes. We aimed to assess whether AE management changed over time and if these modifications impacted on treatment duration and overall survival (OS).

Methods: We analysed the prospectively collected data of 338 consecutive patients who started sorafenib between January 2008 and December 2017 in 3 tertiary care centres in Italy. Patients were divided according to the starting date: Group A (2008–2012; n = 154), and Group B (2013–2017, n = 184). Baseline and follow-up data were compared. In the OS analysis, patients who received second-line treatments were censored when starting the new therapy.

Results: Baseline characteristics, AEs, and radiological response were consistent across groups. Patients in Group B received a lower median daily dose (425 *vs.* 568 mg/day, p <0.001) due to more frequent dose modifications. However, treatment duration was longer (5.8 *vs.* 4.1 months, $p = 0.021$) with a trend toward a higher cumulative dose in Group B. Notably, the OS was also higher (12.0 *vs.* 11.0 months, $p = 0.003$) with a sharp increase in the 2-year survival rate (28.1 *vs.* 18.4%, $p = 0.003$) in Group B. Multivariate time-dependent Cox regression analysis confirmed later period of treatment (2013–2017) as an independent predictor of survival (HR 0.728; 95% CI 0.581–0.937; $p = 0.013$). Unconsidered confounders were unlikely to affect these results at the sensitivity analysis.

Conclusions: Experience in the management of sorafenib-related AEs prolongs treatment duration and survival. This factor should be considered in the design of future randomised clinical trials including a sorafenib treatment arm, as an underestimate of sample size may derive.

Lay summary: Sorafenib has been the standard frontline systemic treatment for hepatocellular carcinoma for over a decade. Its tolerability is limited by different adverse events, which might lead to its permanent discontinuation in a sizeable proportion of patients. After a careful analysis of potential confounders, we demonstrated that the physicians' experience in managing adverse events related to sorafenib has improved over time, with longer treatment periods and less permanent discontinuation for toxicities. More importantly, these improvements also translated into longer patient survival. Our results have relevant repercussions in clinical practice and in the design of future clinical trials.

Introduction

Sorafenib is a multitarget tyrosine kinase inhibitor (TKI) currently used for the treatment of hepatocellular carcinoma (HCC) not amenable to surgery or locoregional treatments.[1] Sorafenib significantly prolongs patients' overall survival (OS), but its use is associated with different adverse events (AEs), mainly dermatological, gastrointestinal and cardiovascular.[2,3] The management of these AEs can require dose reductions and temporary interruptions. In a sizeable proportion of patients, however, these modifications are not able to avoid intolerable or severe AEs, resulting in permanent drug discontinuation.[1] It might seem common sense that the experience accumulated in the prescription of sorafenib could lead to improved management of its related AEs. However, the exact impact of the operators' experience on the prescribing patterns of sorafenib has rarely been investigated.[4] Similarly, it is not known whether this phenomenon can lead to an increase in OS. The latter point is of crucial importance, as dermatological AEs have been demonstrated to have a favourable prognostic impact.[5,6] Thus, avoiding a definitive suspension of sorafenib in these patients would be extremely beneficial. Moreover, data from observational studies[7,8] and randomised clinical trials (RCTs)[9] indirectly seem to suggest that the OS of patients treated with sorafenib is progressively increasing. However, the reasons for this phenomenon have not been fully elucidated. A very recent monocentric study[10] suggested that the management of sorafenib

Keywords: Hepatocellular carcinoma; Sorafenib; Adverse events; Outcome; Prognosis; Learning curve.

Received 24 April 2019; received in revised form 10 July 2019; accepted 2 August 2019; available online 23 August 2019

* Corresponding author. Address: Department of Medical and Surgical Sciences, University of Bologna, Via Massarenti 9, 40136 Bologna, Italy. Tel.: +39 0512142214; fax: +39 0516362725.

E-mail address: francesco.tovoli2@unibo.it (F. Tovoli).

AEs has improved over time, but rigorous multicentric studies that consider time-dependent variables, addressing the possible confounding factor of second-line treatments, and providing a confirmation of the survival benefit through multivariable regressions models are still lacking.

The primary objective of our study was to verify whether the treatment schedules of sorafenib (in terms of average daily dose, duration of treatment, cumulative dose) and the percentage of patients in whom sorafenib was discontinued because of intolerable AEs varied over time. The secondary objective was to verify if these differences had a correlation with the OS after corrections for confounders.

Patients and methods

Design of the study

The present study was performed using the medical records from the databases of Sant'Orsola-Malpighi Hospital, University of Bologna, Italy; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; and Degli Infermi Faenza Hospital, Italy. All of these databases include prospectively collected consecutive patients prescribed with sorafenib and followed up. Data were entered every 3–6 months into electronic data files by co-investigators from each centre taking part and checked at the data management centre for internal consistency. For the purposes of this study, we retrospectively considered patients who were prescribed from January 2008 to December 2017. The starting date coincides with the licensing of sorafenib in Italy, and therefore with the possibility of prescription by all of the study centres. The closing date preceded the licensing of regorafenib in Italy by 1 year and was chosen to allow an adequate follow-up of the patients. For the purpose of this study, the whole 2008–2017 timeframe was divided into 2 equally long periods (January 2008 – December 2012 and January 2013 – December 2017). The closing time for last follow-up was 31 March 2019.

Baseline evaluation

We recorded the following data for each patient at the time of the first prescription of sorafenib: time elapsed since the first diagnosis of HCC, previous treatments for HCC, aetiology of the underlying liver disease, presence/absence of liver cirrhosis, and comorbidities. The main parameters entailing the residual liver function according to the Child-Pugh score were also registered. Finally, we included data about the tumour staging according to the Barcelona Clinic for Liver Cancer (BCLC) classification. The baseline values of alpha-fetoprotein (AFP) were also available for all patients. Patients with HCV-related cirrhosis in sustained virological response after viral eradication with direct-acting antivirals (DAAs) were considered a group of special interest, as recent reports suggested that they might develop a more aggressive form of HCC.[11]

Sorafenib prescription

All patients were prescribed sorafenib at the initial dose of 400 mg twice a day. At the time of the first prescription of sorafenib, all patients were provided with a diary and instructed about the possible sorafenib-related AEs to allow early recognition and treatment. A preventive application of urea cream 20% on hands and feet twice a day, plus loperamide as an over-the-counter medication in case of diarrhoea were recommended. Patients were advised to measure blood pressure every day and to contact their respective centres in case of new symptoms.

Adverse events evaluation and management

New symptoms arising after the treatment start, as well as their timing, were thoroughly recorded. The medical records included both a brief description of each AE as well as its coding according to the Common Terminology Criteria for Adverse Events (CTCAE) used at the time of registration. Since the CTCAE version was upgraded from version 3.0 to version 4.03 in June 2010, all of the AEs occurred before that date were re-codified according to the newer version to allow a correct comparison between groups. Dose modifications in response to the AEs (including dose reductions and dose stops) were performed according to the manufacturer's recommendations. When sorafenib became available in 2008, the dose modifications were performed in strict accordance with the instruction contained in the SHARP protocol.[2] As a result, dose interruptions were extremely limited, and dose reductions below the minimum recommended dose of 400 mg once daily were rare, to aggressively reach the maximum tolerated dose in every single patient at every single moment. Patients who had recurring unmanageable toxicities at the dose of 400 mg once daily were almost invariably discontinued for intolerance. As the experience increased, this approach became less rigid and more patient-tailored. The main aim shifted to identifying, for each patient, a regimen with limited toxicities which could be tolerated on a longer-term basis. For instance, in selected cases, very short dose stops (1–2 days) were performed even for grade 2 toxicities, provided that: a) the patient perceived them as extremely limiting their quality of life; b) the physician regarded these toxicities as a potential threat to the compliance of the patient. Also, if AEs reappeared even after a 7-day dose stop and a subsequent dose reduction to 400 mg once daily, clinicians became more prone to performing a further dose reduction to 200 mg once daily rather than permanently discontinuing sorafenib. This new focus was supported by cumulative evidence, favouring a tailored approach[12,13] and discouraging aggressive treatment re-escalation.[14]

Biochemistry and imaging evaluations

As a general rule, under normal conditions, biochemistry was reassessed every 2 weeks during the first 8 weeks of treatment, then every 4 weeks. The first imaging evaluation of response was scheduled 8–10 weeks after the first dose of sorafenib, with the subsequent radiological controls scheduled every 12 weeks. Computed tomography (CT) of thorax-abdomen-pelvis with iodinated contrast medium was the preferred imaging technique. For patients with contraindications to the iodinated contrast medium, magnetic resonance imaging of the abdomen paired with a high-resolution chest CT was performed. Radiologic evaluation of response during follow-up was done by CT-scan according to the Response Evaluation Criteria In Solid Tumours (RECIST) v1.1.[15] These criteria were preferred over the modified RECIST (mRECIST)[16,17] due to the possible overestimation of tumour necrosis in the setting of systemic treatments by the latter criteria.[18]

Permanent discontinuation of sorafenib

Sorafenib was continued until 1) radiological and clinical progression (for patients eligible for second-line clinical trials, radiological progression alone was considered a sufficient reason for

discontinuation); 2) unacceptable AEs, or; 3) deterioration of liver function. Categorisation into these classes was performed according to the same criteria previously proposed by Iavarone and colleagues.[19] In particular, sorafenib intolerance was defined as the presence of unmanageable grade 2-4 AEs not responding to dose reductions and/or temporary interruption of treatment.[19] In patients who discontinued sorafenib for progression, the impact of the pattern of progression[20] on the post-progression survival was also analysed. Post-progression survival was defined as the time from the last dose of sorafenib to death.

OS evaluation and correlates

OS was measured from the date of starting sorafenib until the date of death. Patients who received a second-line treatment in the setting of clinical trials were censored at the time of the first dose of the new therapy). The rate of long-term survivors, defined as patients with an OS ≥24 months,[7,17] was considered a variable of particular interest. Twelve- and 24-month landmark analyses were performed to further evaluate the long-term modifications of OS. The choice of these cut-offs derived from the most recently described median OS of sorafenib-treated patients in the REFLECT trial[9] and by the recently proposed cut-off to define long-term survivors to sorafenib,[7,21] respectively. The same cut-off values were used in the landmark analyses of a recent ancillary study of the REFLECT trial.[22] To address the possible bias deriving from more second-line RCTs being available in the latest years (resulting in a higher number of censored patients in 1 group), a completeness quantification of the follow-up was performed. Also, a sensitivity analysis was performed to evaluate how strong an unmeasured confounder would have to be to disprove the possibly observed relationship between the period of treatment and OS.

Ethics

The study protocol was reviewed and approved by the local Ethics Committees (Bologna Authority Hospital Ethic Committee for Bologna centre and Romagna Ethic Committee for Meldola and Faenza centres, respectively). All patients gave their written informed consent according to the Ethics Committees' recommendations. The study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistics

Continuous variables are expressed as median and interquartile range. Categorical variables are expressed as frequencies. Group comparisons were performed with the Mann-Whitney *U* test. Categorical variables were evaluated using 2-tailed Fisher's test. Survival curves were estimated using the product-limit method of Kaplan-Meier. The role of stratification factors was analysed with log-rank tests. To define the predictors of OS we used a time-dependent covariates survival approach including statistically significant clinical variables (p <0.05) from the univariate Cox analysis. The completeness quantification of the follow-up was performed according to the C-index, as proposed by Clark *et al.*[23] Briefly, C-index is the ratio of the total observed follow-up years divided by the total potential follow-up years. In the case of our study, the observed follow-up for each patient was the time from study entry to the death or censoring. The potential follow-up for each patient was the time from study entry to the closing date of the study or patient death, whichever came first. The sensitivity analysis was performed calculating the E-value and the limit of its 95% CI closest to the null.[24,25] Statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) (Supplementary CTAT Table).

Results

Study population

This study included 338 patients. Most patients were cirrhotic (96.8%), viral hepatitis was the leading cause of their chronic liver disease (HBV infection: 21.8%, HCV infection 49.7%, non-viral causes 28.5%). One hundred fifty-four patients started sorafenib in the 2008–2012 period (Group A), while the remaining 184 patients began treatment in the 2013–2017 period (Group B).

Baseline characteristics

There were no significant differences in the baseline characteristics between the 2 groups, especially in terms of demographics, liver function, and tumour staging (Table 1). Amongst patients with HCV-related liver disease, the rate of HCV-RNA positive patients was 87.6 and 85.9% in Groups A and B, respectively (p = 0.748). These proportions accounted for 19 and 26 patients in sustained virological response in the first and second period, respectively. All of the 19 patients in the 2008–2012 period had achieved a sustained virological response after interferon-based treatments. Amongst the 26 patients who started sorafenib in the 2013–2017 period, 18 had eradicated the HCV infection with interferon-based treatments and 8 with second-generation DAAs. No patients with HBV-related cirrhosis were HBV-DNA positive at the time of sorafenib prescription. Finally, we found a similar rate of comorbidities in the 2 groups (Table S1).

Follow-up

The median follow-up was 10.5 months (range 0.2–78.9), with no significant differences between study groups (10.3 *vs.* 10.5 months in Groups A and B, respectively). The C-index was 94.0 % in Group A and 85.1% in Group B.

Adverse events evaluation and management

In both groups, almost every patient reported at least 1 AE after sorafenib start (Table 2). Overall, the rate of patients reporting at least 1 dermatological AE (hand-foot skin reaction or skin rash) was similar in the 2 groups (34.4% *vs.* 38.0% in Groups A and B, respectively, p = 0.498). The rate of patients complaining of gastrointestinal symptoms was also similar in the 2 groups (42.9% *vs.* 50.5%, p = 0.189). The prevalence of treatment-related arterial hypertension was 24.8% in Group A and 27.8% in Group B (p = 0.538).

In most patients, the management of AEs required at least 1 dose modification. The rate of patients who required a dose reduction to 400 mg/day was higher in Group B than in Group A (86.4 *vs.* 75.3%, p = 0.009). Re-escalation to a higher dose, however, was possible for a sizeable number of patients in both groups (Table 3) More patients received a dose reduction to 200 mg/day in Group B compared to Group A (30.4 *vs.* 13.6%, p <0.001). In this case, the majority of patients tolerated a dose escalation to 400 mg/day. This refers to the first dose adjustment and not to the number of dose adjustments during follow-up.

A similar number of patients received at least 1 temporary dose stop (87.5 *vs.* 81.2%, p = 0.130). However, the rate of

Table 1. Baseline characteristics of study patients according the period of start of sorafenib.

Variables	2008–2012 period (n = 154)	2013–2017 period (n = 184)	*p* value
Age (years)	70 (62–75)	69 (58–75)	0.334
Males	135 (87.7)	156 (84.3)	0.426
Cirrhosis	149 (96.8)	178 (96.7)	1.000
Etiology			
HBV	37 (24.0)	36 (19.6)	0.354
HCV	75 (48.7)	93 (50.5)	0.745
Non-viral	42 (27.3)	55 (29.9)	0.630
Disease duration			
<6 months	46 (31.2)	70 (39.7)	0.199
6–12months	24 (14.9)	31 (15.8)	
>12 months	84 (53.9)	83 (44.0)	
Bilirubin (mg/dl)	0.91 (0.62–1.26)	0.91 (0.64–1.20)	0.885
Albumin (g/L)	36 (33–39)	36 (33–40)	0.566
INR (ratio)	1.14 (1.06–1.25)	1.13 (1.06–1.23)	0.438
Ascites	13 (8.4)	18 (9.8)	0.709
Encephalopathy	6 (3.9)	4 (2.2)	0.522
Child-Pugh B	11 (7.1)	16 (8.7)	0.690
Tumor stage			
Intermediate (BCLC B)	54 (35.1)	72 (38.2)	0.498
Advanced (BCLC C)	100 (64.9)	112 (61.8)	
Performance status			
0	98 (63.6)	130 (70.7)	0.200
1	56 (36.4)	54 (29.3)	
Macrovascular invasion	50 (32.5)	50 (27.2)	0.339
Extrahepatic spread	51 (33.1)	76 (41.3)	0.143
AFP >400 ng/ml	47 (30.5)	45 (24.5)	0.222
Number of previous TACE procedures			
0	64 (41.6)	82 (44.6)	0.270
1	24 (15.6)	32 (17.4)	
2	28 (18.2)	32 (17.4)	
3	20 (13.0)	18 (9.8)	
4	11 (7.1)	16 (8.7)	
>5	7 (4.5)	4 (2.2)	

Continuous variables are expressed as median (interquartile range). Categorical variables are reported as frequencies (percentage).
AFP, alpha-fetoprotein; BCLC, Barcelona Clinic for Liver Cancer; INR, international normalized ratio; TACE, transarterial chemoembolisation.
Groups were compared with the Mann-Whitney test for categorical variables and the Pearson Chi square test for categorical variables.

Table 2. Prevalence of treatment-emergent adverse events according to the period of start of sorafenib.

Adverse events	2008–2012 period (n = 154)		2013–2017 period (n = 184)	
	All grades	Grade 3	All grades	Grade 3
Any adverse event	151 (98.0)	56 (34.4)	181 (98.1)	61 (33.2)
Fatigue	96 (62.4)	18 (11.9)	133 (72.2)	12 (6.4)
Diarrhea	61 (39.6)	9 (5.9)	86 (46.7)	7 (3.7)
Hand foot skin reaction	45 (29.2)	6 (3.9)	63 (34.3)	14 (7.4)
Hypertension	38 (24.8)	10 (6.5)	51 (27.8)	10 (5.5)
Skin rash	15 (9.7)	3 (1.9)	19 (10.3)	7 (3.8)
Weight loss	15 (9.7)	0	17 (9.2)	2 (0.9)
Hyporexia	13 (8.4)	0	10 (5.4)	0
Nausea	11 (7.1)	2 (1.3)	17 (9.2)	2 (0.9)
Thrombocytopenia	9 (5.8)	2 (1.3)	13 (7.1)	0
Alopecia	8 (5.2)	NA	10 (5.4)	NA
Anaemia	7 (4.5)	2 (1.3)	5 (2.7)	0
Leucopenia	6 (3.9)	2 (1.3)	8 (4.3)	2 (0.9)
Dysphonia	6 (3.9)	0	7 (3.8)	2 (0.9)
Mucositis	5 (3.2)	0	5 (2.7)	0
Epistaxis	2 (1.3)	0	4 (2.2)	1 (0.5)

Data are expressed as frequencies (percentage).

Table 3. Dose modification strategies in response to the treatment-emergent adverse events.

	2008–2012 period (n = 154)	2013–2017 period (n = 184)	*p* value
Dose reduction to 400 mg/day	113 (75.3)	157 (86.4)	0.009
Re-escalation to 800 mg/day	34/113 (30.2)	35/157 (22.0)	0.341
Dose reduction to 200 mg/day	21 (18.2)	56 (35.2)	<0.001
Re-escalation to 400 mg/day	15/21 (71.4)	34/56 (60.7)	0.691

Data are expressed as frequencies (percentage).
Groups were compared with the Fisher test.

patients who received a temporary dose stop in at least 2 different occurrences was higher in Group B compared to Group A (54.3 *vs.* 42.2%, $p = 0.029$).

Imaging evaluation

Fourteen (9.1%) and 15 (8.2%) patients died before the first imaging follow-up in Groups A and B, respectively, in a clinical setting of early progression ($p = 0.846$). A sizeable proportion of this population had a Child-Pugh B class at the baseline (24.1%). Other traditionally negative predictors of survival were also relatively prevalent in this population, such as performance status 1 (48.3%) and AFP >400 ng/ml (41.4%). Instead, the rate of AEs was lower in comparison with the remaining population (dermatological AEs 13.8%, diarrhoea 13.8%, hypertension 17.2%). After the first imaging evaluation, the objective response and the disease control rates were comparable across the study groups (Fig. 1). In particular, the disease control rate was 51.3% in Group A and 56.5% in Group B ($p = 0.688$).

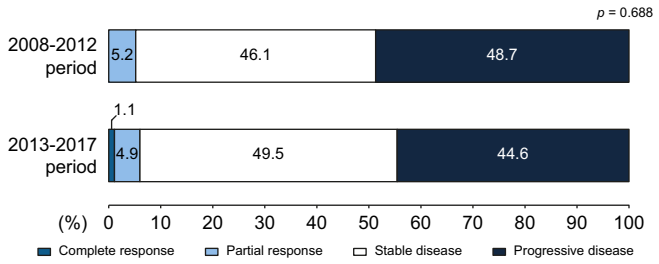


Fig. 1. Radiological response according to the Response Evaluation Criteria in Solid Tumors version 1.1 at the first imaging follow-up first imaging follow-up (performed 8–10 weeks after the start of sorafenib). P was calculated using the Pearson Chi Square test.

Permanent sorafenib discontinuation

During the follow-up, sorafenib was permanently discontinued in all but 4 patients, all of them belonging to the Group B. The median treatment duration was significantly higher in Group B (5.8 *vs.* 4.1 months, $p = 0.021$), with a lower median daily dose (425 *vs.* 568 mg/day, $p < 0.001$) compared to Group A. There was a trend toward a higher cumulative dose in the Group B, which however did not reach statistical significance (75.0 *vs.* 65.6 g, $p = 0.313$). Progression was the main cause of permanent sorafenib discontinuation in both groups (Table 4). Of note, permanent discontinuation due to AEs was significantly higher in Group A compared to Group B (20.8% *vs.* 9.2%, $p < 0.001$). For the 198 patients who had a documented radiological progression at the time of sorafenib discontinuation, the pattern of progression was similar (BCLCp-B 26.2 *vs.* 26.3%; BCLCp-C1 39.3 *vs.* 38.6%; BCLCp-C2 34.5 *vs.* 35.1%) in Group A and B, respectively ($p = 0.994$).

OS evaluation and correlates

The multivariable analysis of factors related to the OS included all clinically statistically significant variables at the univariate analysis, considered for a forward stepwise approach. The multivariable analysis consistently identified Child-Pugh class, performance status, macrovascular invasion, alpha-fetoprotein ≥400 ng/ml, the appearance of dermatological AEs and period of treatment (HR 0.728; 95% CI 0.581–0.937; $p = 0.013$) as independent predictors of OS (Table 5). Extrahepatic spread did not reach the full statistical significance as a predictor of OS in our series ($p = 0.111$). The lack of a significant result was due to the presence of a subgroup of patients with limited extrahepatic spread (18% of all metastatic patients) who achieved long-lasting radiological disease control.

When dividing patients according to their era of treatment, the median OS was significantly higher in Group B compared

Table 4. Reasons leading to sorafenib permanent discontinuation. Groups were compared with the Fisher test.

Reason for discontinuation	2008–2012 period (n = 154)	2013–2017 period (n = 180)*	p value
Progression	98 (63.6)	129 (71.7)	0.127
Intolerance	32 (20.8)	17 (9.4)	<0.001
Liver failure	20 (13.0)	26 (14.4)	0.752
Other	4 (2.6)	8 (4.4)	0.557

* Four patients still receiving sorafenib in this group.

Table 5. Predictors of survival according to the multivariable Cox regression performed using appearance of dermatological adverse events as a time-dependent variable.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p value
Age >70 years	1.190	0.834–1.699	0.337	–	–	–
Male gender	1.034	0.815–1.311	0.784	–	–	–
Viral etiology	1.011	0.722–1.300	0.733	–	–	–
Time since first HCC diagnosis >12 months	0.888	0.789–1.000	0.049	–	–	0.723
Child-Pugh B status	2.638	1.751–3.972	<0.001	2.093	1.364–3.211	0.001
Performance status (0 *vs.* 1)	1.651	1.287–2.118	<0.001	1.357	1.043–1.765	0.023
Macrovascular invasion	1.770	1.373–2.282	<0.001	1.722	1.331–2.622	<0.001
Extrahepatic spread	1.250	0.989–1.584	0.095	–	–	0.111
AFP >400 ng/ml	1.486	1.147–1.924	0.003	1.328	1.024–1.724	0.033
Dermatological adverse events	0.562	0.436–0.725	<0.001	0.624	0.482–0.808	<0.001
Period of treatment (2013–2017 *vs.* 2008–2012)	0.694	0.547–0.880	0.003	0.728	0.581–0.937	0.013

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio.

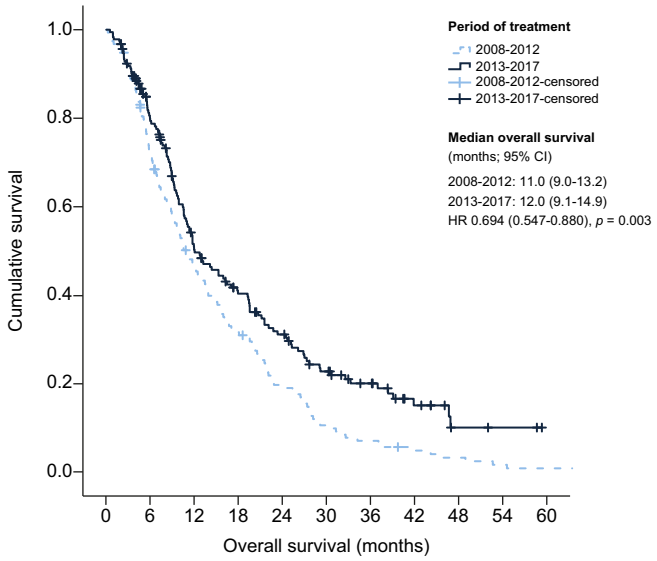


Fig. 2. Overall survival outcomes. The hazard ratio (HR) was calculated using a Cox regression analysis.

to Group A (12.0 *vs.* 11.0 months, $p = 0.002$) (Fig. 2). Notably, the rate of long-term survivors was significantly higher in Group B than in Group A, with a 2-year and 3-year survival rate of 28.1 *vs.* 18.4% ($p = 0.003$) and 14.6 *vs.* 6.8% ($p = 0.037$), respectively. The landmark analysis largely confirmed these findings (Fig. 3). Analysing the patients according to their radiological response, the survival gain was particularly evident for patients who achieved disease control (21.5 *vs.* 19.5 months, $p = 0.009$). On the contrary, OS did not differ across the study groups for patients with progressive disease at their first imaging control (Fig. 4).

The sensitivity analysis reported an E-value of 1.356 for the association between period of treatment and OS. The limit of the 95% CI closest to the null hypothesis was 1.335. These values mean that the observed association between OS and period of treatment could be nullified only by an unmeasured confounder associated with both OS and period, with a strength similar to that of performance status or AFP >400 ng/ml, which is very unlikely to have been missed. On the contrary, a weaker confounder could not disprove this association.

Subgroup analyses

Patients previously treated with direct-acting antivirals

Within the limitations of the reduced sample size (n = 8), patients with HCC post-DAA treatment more frequently presented in the advanced stage (75.0%), but their response to sorafenib was not worse compared to the remaining study population (disease control rate 62.5%). Also, the OS of these patients was not significantly impaired (median 12.0 months).

Patients previously treated with transarterial chemoembolisation

Overall, 58.4 and 55.4% of patients of the Group A and Group B had received at least 1 transarterial chemoembolisation (TACE) before the first dose of sorafenib. As reported in Table 1, there was no difference in the number of TACE procedures ($p = 0.270$). To investigate a possible detrimental effect of repeated TACE, we created 2 different multivariate regressions which included only the subgroup of patients who received at least 1 TACE.

In the first model, we set 2 TACEs as a cut-off (1–2 *vs.* 3 or more TACE). In this case, the number of previous TACEs met a borderline significance at the univariate analysis ($p = 0.083$) and was not confirmed as an independent predictor of survival at the multivariate Cox regression ($p = 0272$).

In the second model, the cut-off was set at 3 TACEs (1–3 *vs.* 4 or more TACE). In this model, the number of previous procedures still met a borderline significance at the univariate analysis ($p = 0.056$), but this time was confirmed as a prognosticator at the multivariate regression (HR 1.595; 95% CI 1.065–2.390; $p = 0.024$).

Notably, the period of treatment was confirmed as an independent predictor of survival both in the first (HR 0.703; 95% CI 0.513–0.963; $p = 0.028$) and in the second model (HR 0.693;

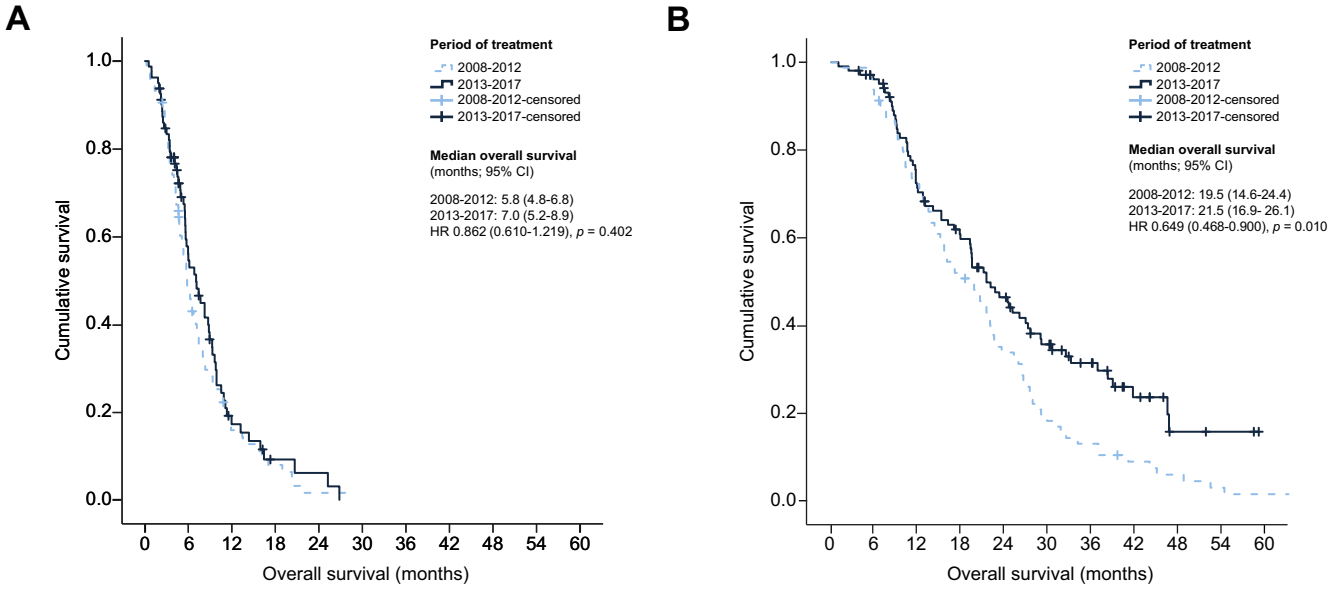


Fig. 3. Overall survival outcomes according to the 12-month and 24-month landmark analyses. (A) 12-month landmark analyses; (B) 24-month landmark analyses. Hazard ratios (HR) were calculated using Cox regression analysis.

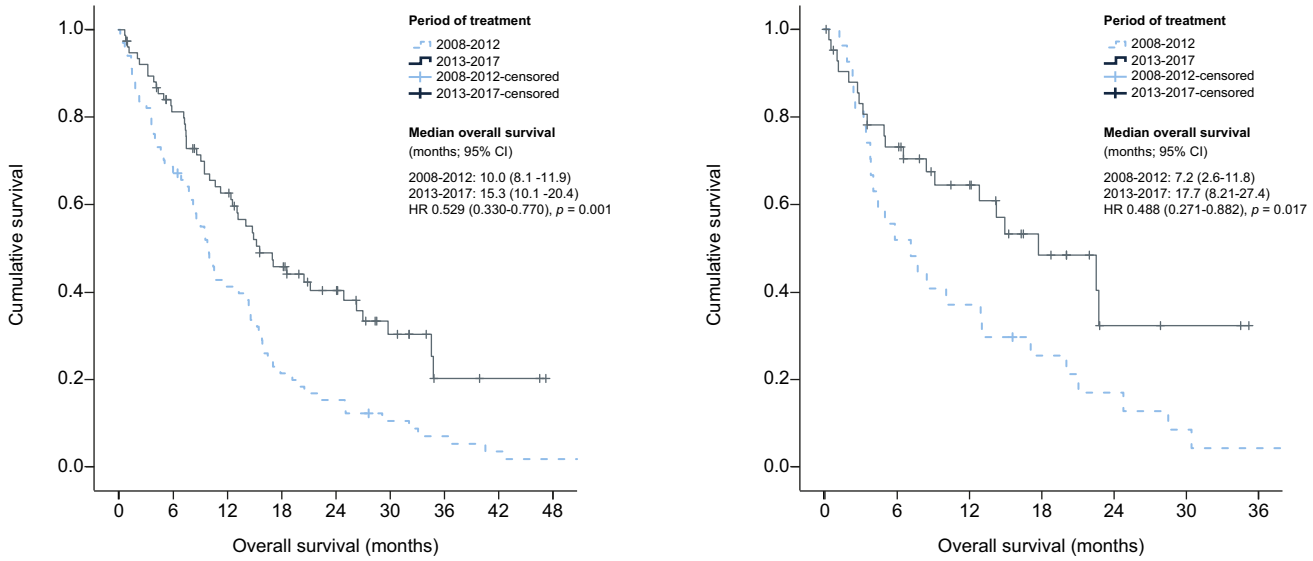


Fig. 4. Overall survival outcomes stratified according to the first imaging response. (A) Progressors and (B) responders. Hazard ratios (HR) were calculated using Cox regression analysis.

95% CI 0.506–0.949; $p = 0.022$) despite the reduced statistical power of the subgroup analyses.

Pattern of progression and post-progression survival

The pattern of progression was significantly correlated with the post-progression survival. The median OS was 11.0 (95% CI 7.4–14.8), 6.0 (95% CI 4.2–7.6), and 4.7 (95% CI 3.4–6.2) months in the BCLCp-B, BCLCp-C1 and BCLCp-C2 classes, respectively (p <0.001). Progression due to new extrahepatic lesion(s) was associated with a significantly worse post-progression survival compared to other patterns of progression (4.9 (95% CI 3.1–6.5) *vs.* 8.0 (95% CI 5.6–10.0) months, p <0.001).

Discussion

We provide direct evidence supporting 2 novel findings. First, the management of sorafenib-related AEs has changed over time, now allowing a longer duration of treatment. Second and most important, these changes also translate into a survival gain.

Regarding the first point, our study provides the first direct confirmation of previously indirect evidence. In the registrative phase III SHARP trial,[2] 38% of patients had to discontinue sorafenib due to intolerable AEs. Subsequent observational studies which enrolled populations in the first 4 years following sorafenib licensing (and therefore comparable to Group A of our study) showed a comparable rate of discontinuation for toxicities. For example, in a large sorafenib field practice study including 296 patients recruited in 2008–2010, this rate was about 40%.[26] In their prospective study on the role of dermatological AEs, Reig *et al.*[5] reported a withdrawal rate for AEs of 30.5% amongst 147 patients enrolled in the 2008–2011 period. This rate was slightly lower (21%) in the real-life GIDEON study (comprising 3,371 patients enrolled in 2009–2012).[8] On the other hand, another large multicentre observational study (INSIGHT) evaluated patients enrolled up to 2014 and described a lower rate of patients with unmanageable intolerance (15.5%).[7] This trend found further indirect confirmation from the second-line clinical trials of ramucirumab (REACH-2) and pembrolizumab (KEYNOTE-224). The rate of patients entering these trials following sorafenib withdrawal for AES was 17.1 and 20.0%, respectively.[27,28] A final clue came from the non-inferiority phase III RCT lenvatinib *vs.* sorafenib (REFLECT), in which only 7% of patients in the sorafenib treatment arm had to discontinue the drug due to AEs.[9]

In addition to the confirmation of this indirect evidence, our study also showed that a reduced interruption rate for AEs corresponds to an extension of the treatment duration. This longer treatment duration in the second period is even more striking if we take into the account the possible interference derived by the absence of approved drugs and the relative paucity of clinical trials in the first period of the study. This different clinical setting, in fact, could have led to longer treatment durations in the first period, as sorafenib could not have been discontinued to offer second-line options, as they were lacking at that time. This data was not inferable from previous observational studies, nor from the comparison of the SHARP and REFLECT data. While treatment beyond radiological progression was allowed in the first trial, progression automatically resulted in permanent treatment discontinuation as of protocol rules in the latter.[2,9] Only very recently, Raoul and colleagues[10] reported similar results in a retrospective single-centre study. Their report of an increase in treatment duration from 4.3 months in 2008–2012 *vs.* 5.9 months in 2013–2017 is strikingly similar to our results. Our study provides a validation of these initial results through a large multicentre collaboration. Of note, more flexible and personalised management of treatment schedules also resulted in a lower median daily dose. This finding should not be seen as a justification for starting treatment at a half dose or to be particularly indulgent with dose reductions and stops. Instead, it was the result of accumulating experience, which led to specific choices under well-defined circumstances, performed to balance the highest tolerable dose with the highest likelihood of achieving long-term compliance. These choices were possible only thanks to a close follow-up after sorafenib initiation, with easy access to unscheduled visits and consultations to detect AEs, manage them promptly, and adjust the dosage. Only in this scenario is it possible to improve treatment

compliance with optimal efficacy, without unneeded treatment interruptions or cancellations.[5]

Most importantly, we demonstrated for the first time that experience in the management of AEs also has an impact on OS. While the median gain may seem modest (about 1 month), it should also be considered that the whole study population also included early progressors, *i.e.* patients for which improvement in the management of AEs is unlikely to mirror into a survival gain (as confirmed by our subgroup analysis). On the contrary, the median survival gain was doubled (about 2 months) in patients who achieved disease control. The difference in the rate of long survivors was even more striking. It can, therefore, be hypothesised that the improved management of AEs in responders reduced the risk of unnecessary drug discontinuation allowing a more extended treatment and a longer OS. So far there has been no direct demonstration of an improvement in the OS of patients treated with sorafenib over time. In the aforementioned study by Raoul *et al.*[10], the OS was in fact significantly higher in the last 5 years (12 *vs.* 8 months) in the univariate analysis, but it was not possible to confirm this result in a multivariate regression analysis. Even indirect evidence about the critical aspect of OS is minimal, deriving mainly from information collected in the REFLECT trial. In this study, the median OS in the sorafenib treatment arm was remarkably superior to that initially reported in the SHARP trial (12.4 *vs.* 10.7 months). However, the REFLECT study excluded patients with unfavourable prognostic factors (neoplastic occupation of the liver >50%, neoplastic thrombosis of the main portal trunk, biliary invasion) and this choice could at least partially justify the apparent improvement in OS. As a consequence, no reliable information about OS modifications were available before our study.

We are aware that analysing a possible period-effect can be tricky due to multiple possible analytical pitfalls and confounders. However, we have reasonable evidence to believe that our results were genuine. First, the baseline characteristics of the patients were similar in the 2 groups in terms of tumour burden, liver function, performance status, comorbidities, and number of previous TACE procedures, making the hypothesis of an improved referral of the patients unlikely as a possible alternative explanation. Second, in a similar line, the duration of treatment and the median daily dose were the only significantly different variables in the follow-up of the 2 groups, thus excluding an imbalance in other confounding factors (for instance, a difference in the pattern of progression). Third, censoring the survival of patients who received second-line treatments excluded that improvements in oncological treatments were the cause of the longer OS. While this choice caused a slightly lower completeness of the follow-up in the second group, the completeness remained very high in absolute terms. Fourth, innovations in non-oncological therapies are an equally unlikely alternative explanation, as demonstrated by both the unmodified OS in non-responder patients and the similar rate of HCV viraemic patients. In this regard, the 8 patients previously treated with DAAs had more frequent onset in the advanced stage, as previously described by Reig *et al.*[11], but their response to sorafenib was not different from that of the remaining study population. Finally, any theoretical confounder not considered in the previous points should have required a very relevant impact on OS to disprove our results, as demonstrated by sensitivity analysis.

In conclusion, the increasing experience with the management of sorafenib-related AEs is leading to longer treatment duration and survival in responders. Our results have immediate implications, both in clinical and research terms. One clinical implication is that a lower discontinuation rate for AEs likely leads to better access to subsequent treatments. Regorafenib, for example, is only available for patients who progressed on sorafenib. At the same time, the improved management of AEs is extremely likely to translate into optimised management of other TKIs (regorafenib, cabozantinib) with a cumulative OS advantage. As for research implications, the increasing median OS has obvious implications in the design of RCTs in which sorafenib is used as a comparator drug. In this case, an OS estimate based on the SHARP trial or early observational studies could lead to an underestimation of the sample size needed to reach a superiority or non-inferiority endpoint. The most immediate examples are the numerous trials of immune-checkpoint inhibitors versus sorafenib in the frontline systemic setting.[29] These trials will be of critical importance in shaping the future therapeutic algorithms for the systemic treatment of HCC in the near future, and their results are eagerly awaited. Therefore, we suggest that the increased survival under sorafenib should be considered in the design of future trials, to minimise the risk of unintentional failure due to an underestimated sample size.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

FT and AG: consultant for Bayer AG. ACG: consultant for Bayer, advisory board for Eisai. FP: consultant for Astrazeneca, Bayer AG, EISAI, GE, Tiziana life sciences; Speaker bureau honoraria: Bayer AG, Bracco, EISAI, Laforce; research contract with Esaote. LI, FGF, GR, GN, GO, and MR: none to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: FT, AG, LI; Data collection: LI, ACG, AG, FGF; Experiments and procedures: GR, GO, GN, MR; Writing and critical revision of the draft: FT, ACG, FP.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.015.

References

Author names in bold designate shared co-first authorship

[1] Forner A, Da Fonseca LG, Díaz-González A, Sanduzzi-Zamparelli M, Reig M, Bruix J. Controversies in the management of hepatocellular carcinoma. JHEP Reports 2019;1:17–29. https://doi.org/10.1016/j.jhepr.2019.02.003.

[2] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.

[3] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34.
[4] Casadei Gardini A, Scarpi E, Foschi FG, Marisi G, Maltoni M, Frassineti GL. Impact of physician experience and multidisciplinary team on clinical outcome in patients receiving sorafenib [in press]. Clin Res Hepatol Gastroenterol 2018. https://doi.org/10.1016/j.clinre.2018.11.005.
[5] **Reig M**, **Torres F**, Rodriguez-Lope C, Forner A, LLarch N, Rimola J, et al. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. J Hepatol 2014;61:318–324.
[6] Díaz-González Á, Sanduzzi-Zamparelli M, Sapena V, Torres F, LLarch N, Iserte G, et al. Systematic review with meta-analysis: the critical role of dermatological events in patients with hepatocellular carcinoma treated with sorafenib. Aliment Pharmacol Ther 2019;49:482–491.
[7] Ganten TM, Stauber RE, Schott E, Malfertheiner P, Buder R, Galle PR, et al. Sorafenib in patients with hepatocellular carcinoma-results of the observational INSIGHT study. Clin Cancer Res 2017;23:5720–5728.
[8] Marrero JA, Kudo M, Venook AP, Ye SL, Bronowicki JP, Chen XP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study. J Hepatol 2016;65:1140–1147.
[9] Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163–1173.
[10] Raoul JL, Adhoute X, Penaranda G, Perrier H, Castellani P, Oules V, et al. Sorafenib: experience and better management of side effects improve overall survival in hepatocellular carcinoma patients: a real-life retrospective analysis [in press]. Liver Cancer 2019. https://doi.org/10.1159/000497161.
[11] **Reig M**, **Mariño Z**, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719–726.
[12] Abbadessa G, Rimassa L, Pressiani T, Carrillo-Infante C, Cucchi E, Santoro A. Optimized management of advanced hepatocellular carcinoma: four long-lasting responses to sorafenib. World J Gastroenterol 2011;17:2450–2453.
[13] Brose MS, Frenette CT, Keefe SM, Stein SM. Management of sorafenib-related adverse events: a clinician's perspective. Semin Oncol 2014;41:S1–S16.
[14] Rimassa L, Pressiani T, Boni C, Carnaghi C, Rota Caremoli E, Fagiuoli S, et al. A phase II randomized dose escalation trial of sorafenib in patients with advanced hepatocellular carcinoma. Oncologist 2013;18:379–380.
[15] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.
[16] Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698–711.
[17] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.
[18] Bruix J, Reig M, Sangro B. Assessment of treatment efficacy in hepatocellular carcinoma: response rate, delay in progression or none of them. J Hepatol 2017;66:1114–1117.
[19] **Iavarone M**, **Cabibbo G**, Biolato M, Della Corte C, Maida M, Barbara M, et al. Predictors of survival in patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. Hepatology 2015;62:784–791.
[20] Reig M, Rimola J, Torres F, Darnell A, Rodriguez-Lope C, Forner A, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology 2013;58:2023–2031.
[21] Sacco R, Granito A, Bargellini I, Zolfino T, Saitta C, Marzi L, et al. Clinical outcomes with long-term sorafenib treatment of patients with hepatocellular carcinoma: a multicenter real-life study. Future Oncol 2018;14:3049–3058.
[22] Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Cheng AL, et al. Analysis of survival and objective response (OR) in patients with hepatocellular carcinoma in a phase III study of lenvatinib (REFLECT). J Clin Oncol 2019;37, [abstr 186].
[23] Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet 2002;359:1309–1310.
[24] Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. Epidemiology 2016;27:368–377.
[25] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–274.
[26] Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al. (SOraFenib Italian Assessment) study group. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology 2011;54:2055–2063.
[27] Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased a-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282–296.
[28] Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE- 224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940–952.
[29] **Tovoli F**, **Casadei-Gardini A**, Benevento F, Piscaglia F. Immunotherapy for hepatocellular carcinoma: A review of potential new drugs based on ongoing clinical studies as of 2019. Dig Liver Dis 2019;51:1067–1073.