Systematic Review

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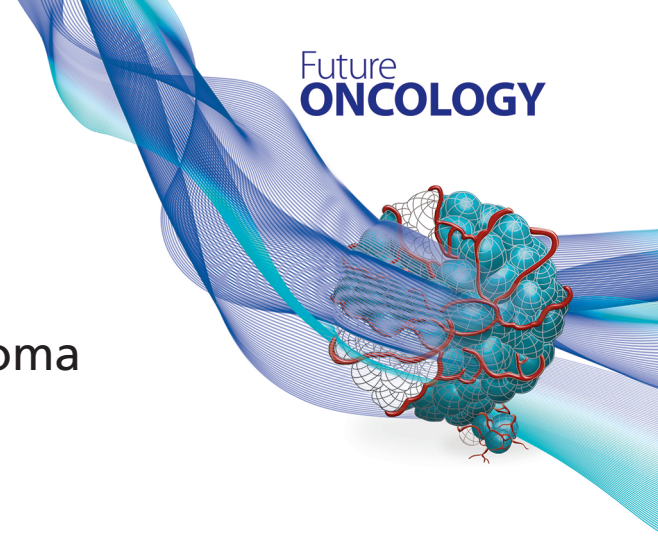

Outcomes of hepatocellular carcinoma patients treated with sorafenib: a meta-analysis of Phase III trials

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Aim: To benchmark overall survival (OS) and time to radiological progression (TTP) of patients enrolled in randomized controlled trials (RCTs) assessing sorafenib in advanced hepatocellular carcinoma using individual participant survival data, and to meta-analyze prognostic factors for OS and TTP. **Methods:** RCTs were identified through literature search until December 2018. Individual participant survival was reconstructed with an algorithm from published Kaplan–Meier curves. **Results:** Ten RCTs were included. Median OS was 10.0 months (95% CI: 9.6–10.5), and median TTP was 4.1 months (95% CI: 3.8–4.3). Multivariable analyses showed HCV positivity, absence of macrovascular invasion and extra-hepatic disease as predictors of longer OS. **Conclusion:** We provided a benchmark for future studies on sorafenib. The present results can be used in the decision making for the early shift to second-line strategy.

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Keywords: hepatocellular carcinoma • meta-regression • sorafenib • survival • systemic therapy • time to progression

Hepatocellular carcinoma (HCC) is a malignancy of global importance that exhibits considerable clinical and biological heterogeneity [1,2] and, in most cases, a dismal prognosis [3]. Despite the extensive application of surveillance programs for the early detection, more than half of HCC patients are diagnosed at a stage for which there are no potentially curative treatment options.

The oral multikinase inhibitor sorafenib is recommended as the standard first-line systemic therapy for compensated patients with advanced HCC and for those with an intermediate HCC deemed unfit for, or who fails to respond to loco-regional therapies [3,4]. Two Phase III randomized controlled trials (RCTs) showed a significant advantage in terms of survival against placebo [4,5]. Since its successful approval, several systemic and intra-arterial therapies have been tested against sorafenib in the first-line (either in noninferiority or in superiority trials) [6] or in the second-line settings [7]. Among these, as first-line therapies only lenvatinib RCT [8] met its (noninferiority) end point, whereas regorafenib [9], cabozantinib [10] and ramucirumab [11] showed survival benefit against placebo for patients in the second line setting.

Efficacy and cost–effectiveness of sorafenib for HCC have been widely assessed in clinical practice [12–14] showing that treatment with sorafenib is characterized by high rates of anticipated discontinuation caused by tumor progression, liver decompensation and adverse events (AEs) both in RCTs [4,5] and in field practice studies [12,15,16]. Molecular predictors of response are still lacking and the determination of the optimal point at which to move from first- to second-line therapy is a major goal in the management of these patients. Important questions still remain: 'which is the best time to switch from sorafenib to second-line systemic therapy?' as well as 'what are the most determinants of tumor progression?'. An accurate estimation of death and risks of progression among these

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patients is essential for assessing therapeutic effect of any new treatment strategy, for calculating sample sizes and interpreting results of second line clinical trials, as well as for cost–effectiveness analysis purposes.

To develop a more comprehensive picture of sorafenib benefit and to increase statistical power for future study designs, we present there a meta-analysis of available high-level evidences by using reconstructed 'individual participant (IP) survival data' of Phase III RCTs. The main aim was to provide a robust benchmark of survival figures achievable with sorafenib treatment and eventually identify possible predictors of death and tumor progression.

Methods

Structure of the study

The term 'individual participant data' (IPD) relates to the data recorded for each participant in a study and, as with any meta-analysis, an IPD meta-analysis aims to summarize the evidence on a particular clinical question from multiple related studies [17]. Unfortunately, despite calls for increased access to IPD from clinical trials, progress toward this is frustratingly slow [18]. We obtained IP survival data through the reconstruction of survival data from the published Kaplan–Meier curves [19]. Subsequently, we applied a one-step meta-analytic approach to preserve the clustering of patients within studies and to implement the estimate of the effect of potential clinical features on the outcome of interest [17].

The present meta-analysis was therefore organized as follows: identify available Phase III RCTs evaluating sorafenib as first-line therapy for intermediate/advanced HCC; reconstruct IP survival data from published Kaplan–Meier curves using an appropriate algorithm; apply a flexible parametric survival model which allows for study clustering.

Identification of eligible studies

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [20].

A systematic search of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases was performed for articles published up to 31 December 2018 with no lower date limit, including the following key words: 'HCC', 'sorafenib', 'RCTs'. Details of the literature search strategy and quality assessment can be found in the Supplementary File 1. Studies were included in the analysis if: they were Phase III RCTs comparing sorafenib as mono-therapy with placebo or any other therapy; they included advanced HCC patients with or without extra-hepatic disease, or intermediate HCCs deemed unfit or failing locoregional therapies; overall survival (OS) and/or time to radiological progression (TTP) were assessed as outcome measures of the effect of the treatment since randomization; and they had been published as full-length articles. Reasons for exclusion from the present study are detailed in the Figure 1. We evaluated the methodological quality of the included studies using five criteria (Supplementary Table 1), as established by Jadad *et al.* [21], Bañares *et al.* [22] and by the Panel of Experts in HCC-design clinical trials [23]. We assessed the quality of trials according to each separate component, with a maximum possible score of ten points. Studies published only in abstract form were excluded because the methodological quality can not be assessed.

Reconstruction of IP survival data

To reconstruct IP survival, the algorithm provided by Guyot *et al.* was applied [19]. This algorithm returns a list of 'participants' with a predicted survival time together with the predicted event of interest (i.e., alive or death; progression or no progression) and showed an excellent accuracy for survival probabilities and medians. Briefly, the algorithm uses the digitalized data on survival probabilities, time and total number of patients, and events to find numerical solutions to the inverted Kaplan–Meier equations. Data were digitalized using Engauge Digitize (version 10.4), a free open source tool for extracting numeric data from images or graphs. The algorithm was implemented in R (version 3.4.3; R Core Team (2013). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Each reconstructed survival curve, either OS or TTP, was visually inspected for accuracy with respect to the original published Kaplan–Meier by overlapping the obtained curve with the published one and by comparing median OS/TTP published with those reconstructed.

To provide further calibration of reconstructed OS, the obtained median values were compared with the pooled median calculated with the method provided by Combescure *et al.* [24]. This approach returns a distribution-free summary survival curve by expanding the product-limit estimator of survival for aggregated survival data. This

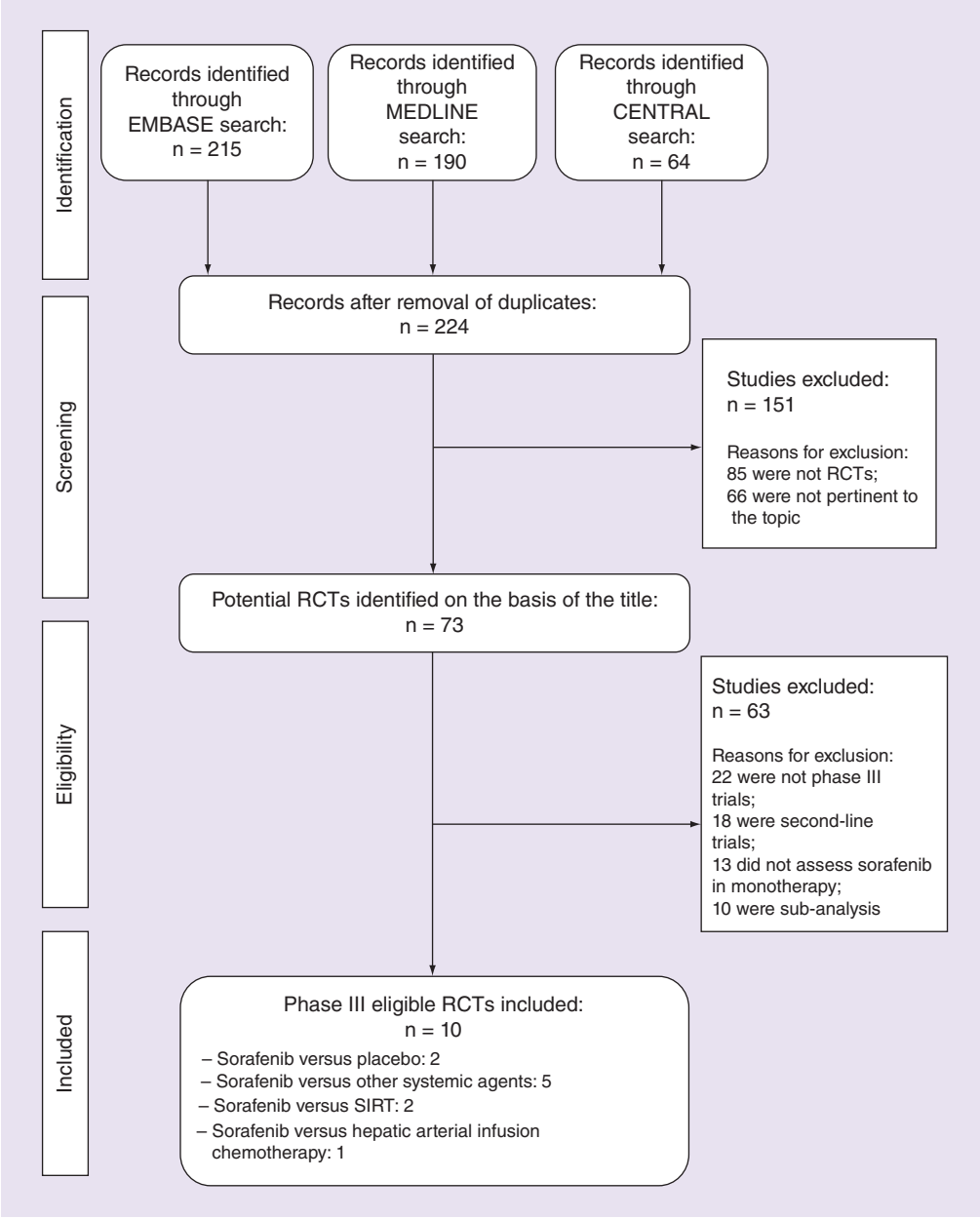

Figure 1. Study flowchart.
RCT: Randomized controlled trial; SIRT: Selective internal radiation therapy.

approach was implemented in R and used package 'metasurv', which contains the data extracted from already published survival rates of untreated patients in randomized clinical trials of HCC [1].

Application of survival model to IPD

Once IP survival data were obtained, common Kaplan–Meier curves were plotted. Subsequently, the average value of included moderators was added to the reconstructed data. Since no specific IPD on moderators was available, we were forced to model a 'frailty' survival model in a one-step approach. A flexible parametric approach was chosen because it more accurately models survival avoiding the proportional hazard assumption, through the application of splines (knots).

For mortality, knots were placed at 3, 6, 9 and 12 months, and for progression knots were placed at 1, 3 and 6 months since randomization. Frailty accounted for study clustering returning a measure for unobserved

Table 1. Main characteristics of patients receiving sorafenib in the Phase III trials included in the meta-analysis.

Study (year)	Versus	n	Age, years (SD)	HCV+ (%)	CTP-A (%)	ECOG-0 (%)	MaVI+ (%)	EHD+ (%)	BCLC-C (%)	Quality	Ref.
Llovet *et al.* (2008)	Placebo	299	64.9 (11.2)	29.1	95.0	53.8	36.1	53.2	81.6	10	[4]
Cheng *et al.* (2009)	Placebo	150	52.8 (18.2)†	10.7	97.3	25.3	36.0	68.7	95.3	10	[5]
Johnson *et al.* (2013)	Brivanib	578	58.5 (18.5)†	20.6	91.9	60.9	27.3	50.3	77.7	9	[24]
Cheng *et al.* (2013)	Sunitinib	544	55.0 (19.0)†	21.9	99.8	53.5	30.5	64.9	83.5	8	[25]
Cainap *et al.* (2015)	Linifanib	521	57.5 (18.5)†	24.8	94.6	66.0	40.5	56.8	80.2	4	[26]
Zhu *et al.* (2015)	+Erlotinib	358	NA	23.5	100	60.3	42.7	61.2	86.6	10	[27]
Kudo *et al.* (2018)	Lenvatinib	476	58.5 (19.0)†	26.0	99.0	63.0	19.0	62.0	81.0	8	[8]
Villgrain *et al.* (2018)	SIRT	222	65.3 (11.2)†	22.1	84.2	62.6	57.7	0.0	67.1	6	[28]
Chow *et al.* (2018)	SIRT	178	57.7 (10.6)	13.5	89.9	79.2	30.3	0.0	44.9	8	[29]
Kudo *et al.* (2018)	+HAIC	103	68.1 (9.1)	45.0	90.0	88.0	62.0	25.0	74.0	8	[30]

† Calculated from median and range using the formula proposed by Wan [32].
The manuscript from Zhu *et al.* did not report ranges to estimate the mean and the SD of patient age.
CTP: Child-Turcotte-Pugh; ECOG: Eastern Cooperative Oncology Group; EHD: Extra-hepatic disease; HAIC: Hepatic arterial infusion chemotherapy; MaVI: Macroscopic vascular invasion; NA: Not available/not assessable; SD: Standard deviation; SIRT: Selective internal radiation therapy.

Table 2. Pooled results of clinical and tumoral features considered as potential moderators for overall survival and time-to-radiological progression in the flexible parametric survival model.

Parameter	Number of at-risk patients	Estimate (95% CI)	I^2	Ref.
Clinical features				
Hepatitis C positive (%)	3429	22.9 (19.3–27.0)	85.2%	[4,5,8,23–29]
Child–Pugh A (%)	3429	95.4 (92.3–97.2)	88.3%	[4,5,8,23–29]
ECOG–0 (%)	3429	61.8 (54.8–68.3)	93.6%	[4,5,8,23–29]
Tumor features				
Macrovascular invasion (%)	3429	37.3 (30.2–44.9)	94.6%	[4,5,8,23–29]
Extra-hepatic disease (%)	3429	52.4 (44.9–59.8)	92.3%	[4,5,8,23–29]
BCLC–C (%)	3429	78.9 (72.1–84.4)	94.4%	[4,5,8,23–29]

Meta-analysis results are reported as pooled estimates and 95% confidence intervals; continuous variables are reported as weighted means and categorical variables as weighted proportions.
I^2 values of <25% were interpreted as low heterogeneity, between 25 and 50% as medium, between 50 and 75% as substantial and above 75% as considerable.
BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group.

heterogeneity that occurs because some unexplained observations are more failure prone (more 'frail') than other observations in the dataset. Frailty was here group-specific, generated by each of the study included. The parametric frailty model was implemented in STATA (StataCorp. 2015. Stata Statistical Software: Release 14, StataCorp LP, TX, USA).

Results

Literature search results

A total of 224 articles were identified using our search criteria for screening (Figure 1). Following the adopted exclusion criteria, 10 Phase III RCTs were retained (Table 1) [4,5,8,25–31]. Of the 10 RCTs, two compared sorafenib with placebo [4,5], five compared sorafenib with other systemic agents [8,25–28], two compared sorafenib with selective internal radiation therapy [29,30], and one with sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy [31]. The risk of bias according to the Jadad tool was graded as 'low' for most of domains (Supplementary Table 2).

Characteristics of included patients

The pooled study cohort consisted of 3429 individual HCC patients fulfilling eligibility criteria and receiving sorafenib. Meta-analysis of clinical and tumor features considered as potential moderators in the successive survival analysis are reported in Table 2. As can be noted, pooled estimates showed a considerable degree of heterogeneity for all potential moderators ($I^2 > 75\%$) supporting the different role of each feature in producing a different outcome in terms of OS and TTP.

Table 3. Comparison between published median values of overall survival and time-to-progression and those based on reconstructed individual participant data.

Study (year)	Median OS (months; 95% CI)		Median TTP (months; 95% CI)		Ref.
	Published	Reconstructed	Published	Reconstructed	
Llovet *et al.* (2008)	10.7 (9.4–13.3)	10.7 (9.1–12.1)	5.5 (4.1–6.9)	5.5 (4.2–6.9)	[4]
Cheng *et al.* (2009)	6.5 (5.6–7.6)	6.5 (5.2–7.7)	2.8 (2.6–3.6)	2.8 (2.6–3.0)	[5]
Johnson *et al.* (2013)	9.9 (8.5–11.5)	9.9 (8.8–10.9)	4.1 (3.1–4.2)	4.1 (3.6–4.5)	[24]
Cheng *et al.* (2013)	10.2 (8.9–11.4)	10.3 (9.1–11.4)	3.8 (2.9–4.2)	3.9 (3.5–4.3)	[25]
Cainap *et al.* (2015)	9.8 (8.3–11.0)	9.8 (8.8–10.9)	4.0 (2.8–4.2)	4.1 (3.5–4.7)	[26]
Zhu *et al.* (2015)	8.5 (7.4–10.6)	8.6 (7.0–10.2)	4.0 (2.9–4.5)	4.0 (3.3–4.7)	[27]
Kudo *et al.* (2018)	12.3 (10.4–13.9)	12.3 (10.6–14.0)	3.7 (3.6–5.4)	Na	[8]
Villgrain *et al.* (2018)	9.9 (8.7–11.4)	9.9 (8.7–11.2)	Na	Na	[28]
Chow *et al.* (2018)	10.0 (8.6–13.8)	10.1 (7.5–14.9)	5.4 (4.1–5.7)	5.4 (4.7–6.1)	[29]
Kudo *et al.* (2018)	11.5 (8.2–14.8)	11.4 (9.6–10.6)	3.5 (3.9–6.7)	3.5 (2.8–4.6)	[30]

The first study from Kudo *et al.* [8]. reported the median TTP in the text but not the corresponding curve, thus, reconstruction was unfeasible. The study from Villgrain *et al.* [28] did not report median TTP; additionally, for estimation of TTP a competing-risk analysis was adopted, thus, making impossible to reconstruct, and validate, any TTP curve.
OS: Overall survival.

The size of the sorafenib arms in each study ranged from 103 [31] to 578 patients [25]. The mean patient age ranges from 52.8 [5] to 68.1 years [31]. The proportion of patients with HCV-related HCC ranged from 10.7 [5] to 44.7% [31]. The percentage of Child–Pugh A patients ranged from 84.2 [29] to 100% [31], while the frequency of an ECOG-PS = 0 went from 25.3 [5] to 88.3% [31]. The proportion of patients with macrovascular invasion (MaVI), as well as with extra-hepatic disease (EHD) differed greatly among the trials, ranging from 18.9 [8] to 62.2% [31], and from 0 [29,31] (in the two RCTs comparing Sorafenib vs selective internal radiation therapy) with 68.7% [5], respectively.

Methodological quality scores varied from 4 [27] to 10 [4,5,28] on a scale of 2 to 10 (Supplementary Table 2). All included trials reported an adequate efficacy of randomization, while an adequate follow-up was not reported in only two studies [25,27]. Blinding was adequate in four RCTs [4,5,25,28]. A high-quality score (≥6 points) was observed in nine trials (90%) [4,5,8,25,26,28–31].

The comparison between published OS and TTP median values and those based on reconstructed IP survival data are reported in Table 3. As can be noted, reconstructed medians were really similar, if not identical, to those reported in each of the study included. Confidence intervals were also quite similar each other providing robustness to reconstructed IP survival data. The complete list of the 3429 patients with reconstructed survival data is available in Supplementary File 2 (Reconstructed IP survival data).

Overall survival

The entire OS curve using IP survival data of 3429 patients is reported in Figure 2, Panel A. The median OS calculated by this way was 10.0 months (95% CI: 9.6–10.5). This figure was very similar to the median calculated by pooling each OS curve (Combescure approach) of 9.9 months [24], albeit with slightly wider confidence intervals in the latter (95% CI: 8.9–11.0). In both cases, median survivals were significantly higher (Log-rank $p < 0.001$) than the pooled median of 5.7 months (95% CI: 4.5–6.7) already calculated for untreated 1813 HCC patients enrolled in RCTs of palliative treatments (Figure 3) [1].

Results from frailty survival models are reported in Table 4. On multivariable analysis, it was observed that positivity for HCV significantly defined a group of patients with better OS ($p = 0.001$), and that the presence of MaVI and EHD determined significant worse prognosis ($p = 0.001$ in both cases). The frailty model returned a θ with $p = 0.119$, indicating that these features accounted for the majority of overdispersion due to variables not accounted for within-study level.

Time to radiological progression

Reconstruction of IP data for TTP was feasible for 2731 patients, since Kudo *et al.* [8]. and Villgrain *et al.* [29]. did not provide necessary data or curves in their manuscripts. The reconstructed TTP curve is reported in Figure 2, Panel B. The median TTP calculated through IPD was of 4.1 months (95% CI: 3.8–4.3), again, a figure very similar to the median obtained by pooling each TTP curve of 4.2 months (95% CI: 3.7–4.7).

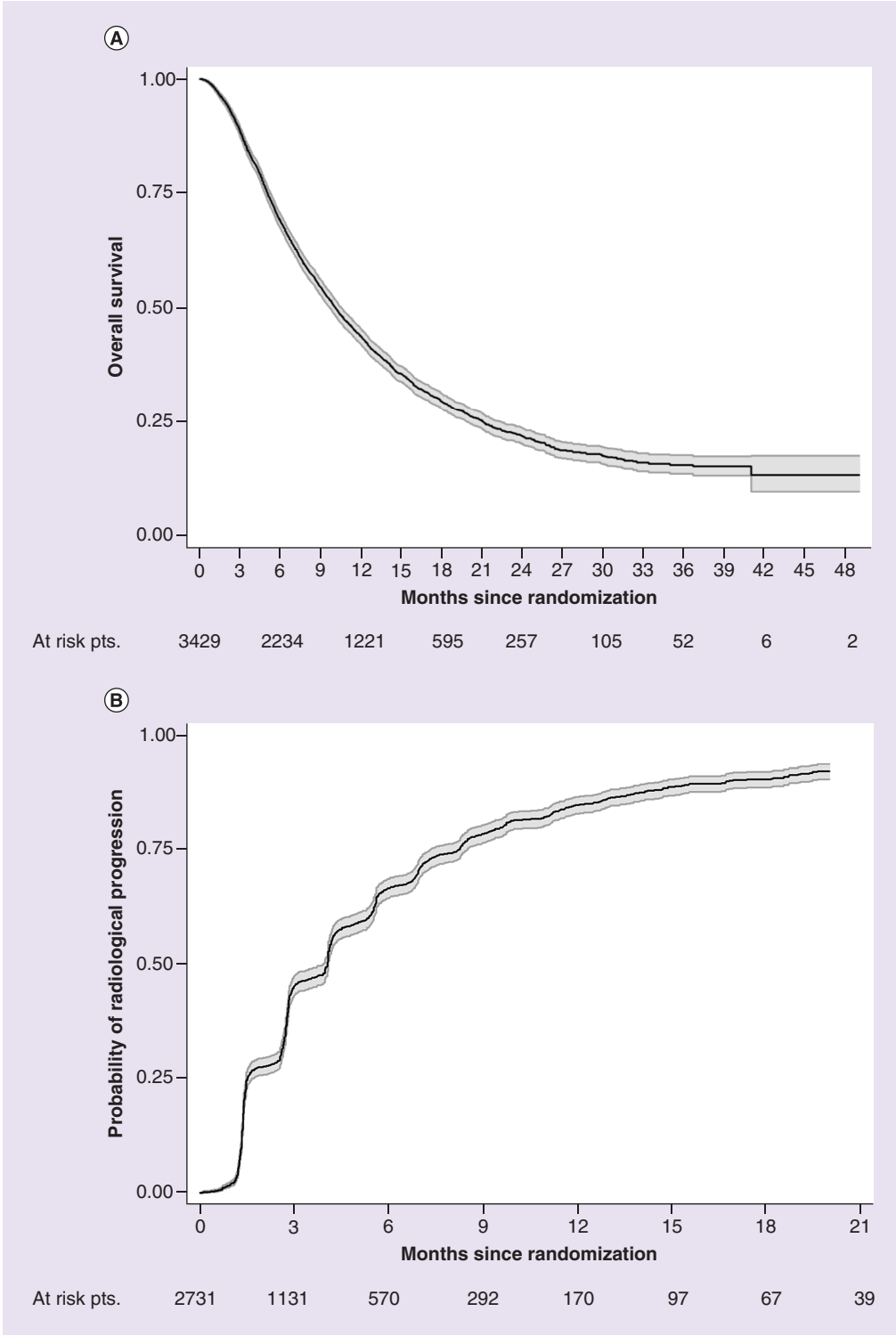

Figure 2. Kaplan–Meier curves reporting outcomes of patients with intermediate/advanced hepatocellular carcinoma treated with sorafenib deriving from individual participant survival data: overall survival of 3429 patients (A) and time to radiological progression of 2731 patients (B).
HCC: Hepatocellular carcinoma; OS: Overall survival.

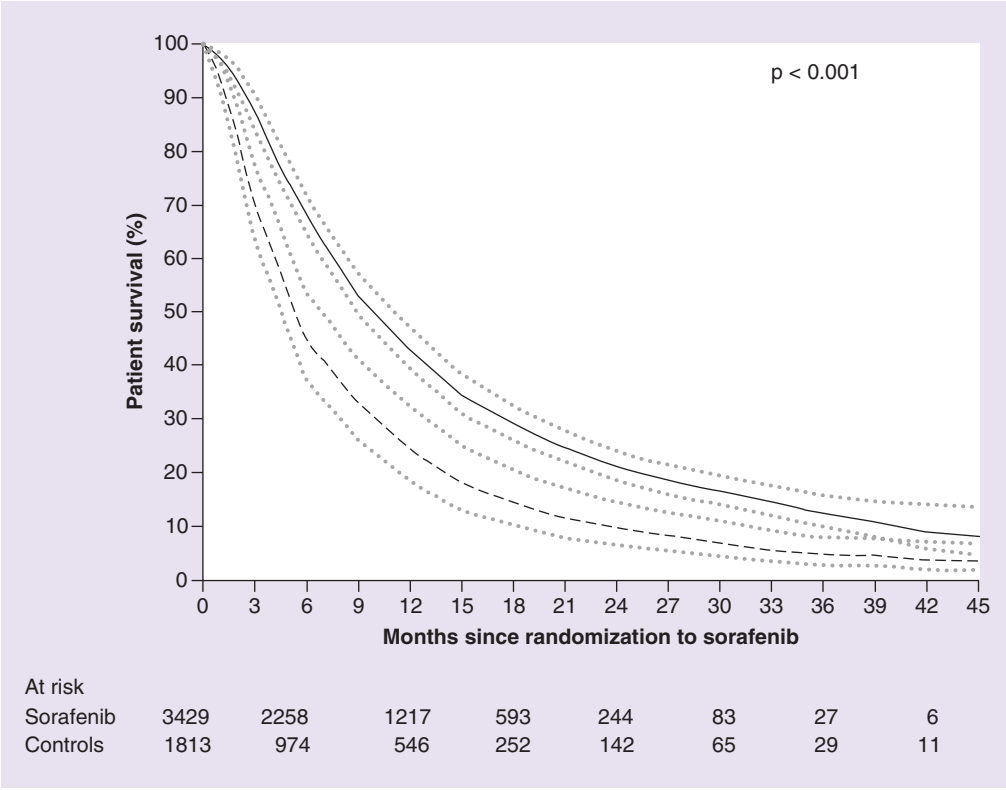

Figure 3. Comparison of overall survival estimates between 3429 patients treated with sorafenib and 1813 untreated hepatocellular carcinoma patients, using aggregate data through Combescure approach. The black solid line refers to patients treated with Sorafenib. The black dashed line refers to untreated hepatocellular carcinoma patients. The blue dotted lines refer to confidence intervals of the two curves.
OS: Overall survival.

Table 4. Results from frailty flexible parametric survival model incorporating splines.

	Hazard ratio (95% CI)	p-value
Mortality		
HCV+ (%)	0.095 (0.038–0.234)	**0.001**
CTP A (%)	0.257 (0.328–2.015)	0.196
ECOG–0 (%)	1.308 (0.664–2.577)	0.438
MaVI+ (%)	4.590 (2.593–8.125)	**0.001**
EHD+ (%)	1.667 (1.262–2.202)	**0.001**
θ (frailty variance)	0.002 (0.001–0.023)	0.119
Progression		
HCV+ (%)	0.223 (0.049–1.015)	0.052
CTP A (%)	0.198 (0.006–6.455)	0.363
ECOG–0 (%)	0.854 (0.267–2.726)	0.790
MaVI+ (%)	4.772 (1.162–19.59)	**0.030**
EHD+ (%)	1.553 (1.044–2.310)	**0.029**
θ (frailty variance)	0.008 (0.001–0.467)	0.041

Note: Bold entries refer to statistically significant associations.
Only variables available for all the studies included were analyzed. BCLC-C was not entered to avoid collinearity with its components (CTP, ECOG, MaVI and EHD)
For mortality, knots were placed at 3, 6, 9 and 12 months. For progression knots were placed at 1, 3 and 6 months. Splines were always statistically significant ($p < 0.05$).
θ represents the estimated variance of frailty at the study level. The corresponding p-values (Prob>= chibar2) verify whether a significant variance component is still present after inclusion of covariates. In other words, the coefficient θ is a multiplicative random factor accounting for overdispersion of model fit due to lack of variable measurements that can vary within each of the study included (so-called 'shared frailty').
CTP: Child-Turcotte-Pugh; ECOG: Eastern Cooperative Oncology Group; EHD: Extra-hepatic disease; MaVI: Macrovascular invasion.

Results from frailty survival models are reported in Table 4. On the multivariable analysis, presence of MaVI and EHD were the only variables significantly associated with rapid progression (p = 0.001 in both cases). The frailty model returned a significant θ value (p = 0.041) indicating that a significant heterogeneity was still present due to within-study variance.

Discussion

According to EASL HCC guidelines [3], sorafenib is recommended as the standard first-line systemic therapy for compensated patients with advanced HCC and for those with an intermediate HCC deemed unfit for, or who fail to respond to, locoregional therapies. In this study, we performed a meta-analysis of aggregate survival data of single sorafenib arms from ten Phase III RCTs published when comparing placebo versus sorafenib and different first-line therapies versus sorafenib as the standard of care for intermediate/advanced HCC. Our data revealed an IP survival of 10.0 months and an IP median time to radiological progression of 4.1 months for sorafenib. To the very best of our knowledge, the present one is the largest (>3000 individuals) and updated attempt to produce such an IPD analyses in this clinical scenario.

The actuarial curve of OS obtained in this meta-analysis (Figure 2) can be considered a useful reference for determining the sample size of future first-line systemic RCTs comparing new agents versus sorafenib, and for obtaining indirect comparisons among different trials estimating drug efficacy. Similarly, our actuarial curve of TTP represents the strongest estimate available to date regarding the risk of radiological progression, providing another useful benchmark for suggesting the more appropriate time for stopping sorafenib and starting second-line agents. As already stated, we provide as supporting excel file (Supplementary File 2) the complete list of the 3429 patients with reconstructed survival data. The free access to these data returns the possibility for its use in further specific analyses.

As expected, different studies included different proportions of potential determinants for progression and survival. The considerable heterogeneity observed among potential moderators (Table 2) inevitably translates into the different survival figures reported in each RCTs, with median OS and TTP rates ranging from 6.5 to 12.3 months and from 2.8 to 5.5 months, respectively (Table 3). Despite the final number of included patients in the IPD analysis was large enough to suggest some strength, the confidence intervals of median OS and median TTP were not particularly narrowed after the IPD analysis in respect to that of each single RCTs. However, within the present analytical framework, this heterogeneity returns the unique possibility to apply a one-stage IPD meta-analysis using potential moderators, at their average values, as determinants of outcome.

With the preservation of study clustering, it was observed at multivariate analysis for OS, that absence of MaVI and EHD, and presence of HCV etiology were the only significant predictors of longer survival. The two tumor individual parameters, both included in the BCLC classification (which was excluded for evident co-linearity), largely explain why this staging system provides accurate information on prognosis in the setting of intermediate/advanced HCC and confirm that tumor burden at baseline has a relevant impact on survival in HCC patients. Moreover, this finding is consistent with the results of SOFIA [12] and ITA.LI.CA. [33] cohorts, which showed, in-field practice setting, a relevant role of baseline tumor burden during sorafenib treatment. We also found that HCV etiology is a robust predictor of survival in HCC patients receiving sorafenib. Considering that: this finding is consistent with results of two recent studies suggesting that the magnitude of survival benefit is greater in HCV patients [34,35]; HCV etiology was a favorable prognostic factor for survival in untreated advanced HCC patients [1]; and finally that, given the positive impact on decompensation and survival due to HCV eradication by direct antiviral agents also in HCC patients [36–39], we can suggest to early shift to second-line therapies in non-HCV-related HCC patients.

According to tumor-related variables, we found, as expected, that MaVI and EHD were independent predictors of radiologic progression of HCC during therapy. These findings may help to: stratify patients according to these HCC pretreatment features in future clinical studies and suggest an early shift to second-line therapies, for those patients with these unfavorable tumor features who do not have clear evidence for response to sorafenib therapy.

According to liver-related variables, field-practice studies showed that sorafenib is frequently administered also in patients with Child–Pugh class B and that OS of patients treated with sorafenib is longer in patients with Child–Pugh class A in comparison with those in class B [12,40]. We did not observe a significant impact of Child–Pugh class on OS, but it should be considered that in our meta-analysis the pooled estimated prevalence of Child–Pugh class A was 95%. RCTs often excluded patients with more advanced liver disease, in those the progression of cirrhosis toward liver decompensation represents a competitive risk for death.

The methodology of the current study could be affected by the potential limitation of the generalizability of its results to new populations and settings, as typically occurs in all meta-analyses. The included studies were performed in highly specialized centres, both in Eastern and in Western areas. Although the overall sample size of patients analyzed exceeded 3000, drawing firm conclusions may be premature. Heterogeneity in baseline severity of illness (with or without extra-hepatic spread and/or MaVI), etiology (HBV, HCV, alcohol), and number and type of prior therapy, may limit the accuracy of our results. We included patient- and study-level covariates to attempt to control these differences. However, our study is limited by the patient-level covariates reported in each of the studies, which were not consistent across trials. Therefore, it should be underlined that these summary results are able to only describe the heterogeneity between studies but not the heterogeneity between patients, considering that they reflect group averages rather than true individual data for potential moderators.

Moreover, we did not control for other potentially important confounders (i.e., microscopic vascular invasion, histological grading and gene profiling) for which data are lacking and this could have affected our results [2]. However, we underline that despite the unavailability of individual data for covariates of each patient included in the meta-analysis, we were still able to analyze progression and survival in a flexible mode. This approach most fits survival trends, and return low values for frailty variance [41].

The available evidence from this meta-analysis of aggregate data enabling us to assess outcomes as time-dependent events is sufficient to conclude that in patients with intermediate/advanced HCC treated with sorafenib: the median OS (10.0 months) and the median TTP (4.1 months) pooled actuarial probability are extremely variable, and no single clinical or tumor characteristic can fully explain this heterogeneity; absence of MaVI and EHD, and HCV etiology are associated with a higher likelihood of survival; HCC patients with etiology other than HCV should early shift to second-line therapies; and presence of MaVI and EHD are predictors of tumor progression.

These pooled reported actuarial OS and TTP probabilities provide a useful benchmark for indirect comparisons of the benefit of new first-line agents for the treatment of advanced HCC, and to better define the correct sequential treatment with second-line agents after failure of sorafenib.

Future perspective

The identification of predictors of survival and progression in patients with HCC is crucial to switch from one treatment to another, and this choice may occur several times throughout the history of patients with HCC. First, in patients with intermediate HCC who received repeated locoregional treatments, it is not clear what is the best time to shift from locoregional to systemic therapy. Subsequently, once the patient has been judged unfit to locoregional treatment, physicians are faced with the choice to start sorafenib or lenvatinib as first-line systemic strategy. Finally, patients with compensated cirrhosis who experienced HCC progression or adverse events to first-line therapy can be shifted to a second-line treatment. To date, four drugs have been approved in the second-line setting: regorafenib (in patients without adverse events to sorafenib), cabozantinib, ramucirumab (in patients with high alfa-fetoprotein levels) and nivolumab (the first immunotherapy approved for HCC). All these drugs have been tested in patients previously treated with sorafenib and there are no second-line RCTs conducted in patients previously treated with lenvatinib. Unfortunately, which second line is the best and which patients will be able to tolerate several lines of therapy remain to be clarified.

Nowadays, physicians could answer these questions in daily clinical practice by basing their decisions on the inclusion criteria of the trials, and on expected toxicities. However, care should be taken in translating trial data into real-world practice. In the future, identification of individual patient factors is needed to guide the choice of the most appropriate treatment sequence and to select subgroups of patients who can obtain the most benefit from immunotherapy. A meta-analysis of individual patient data could provide an accurate treatment comparison in the setting of advanced HCC, in whom a significant heterogeneity is present; decision modeling could be another methodological tool to rank different sequential strategies. Finally, the increase in the number of available treatments makes urgently necessary to identify biomarkers and mechanisms of resistance that could guide the choice of which therapy and when to shift into the sequence.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2019-0287

Author contributions

G Cabibbo, A Cucchetti, C Cammà, AC Gardini, C Celsa, GE Rizzo, P Johnson and G Ercolani take full responsibility for the study design, data analysis and interpretation and preparation of the manuscript. All authors were involved in planning the analysis and drafting the manuscript. All authors approved the final draft manuscript.

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Summary points

- Sorafenib is the recommended first-line systemic therapy for compensated patients with advanced hepatocellular carcinoma (HCC) or intermediate HCC unfit for, or who failed locoregional therapies.
- Molecular predictors of response to sorafenib are lacking and the determination of the optimal point at which to move from first to second-line therapy remains not clear.
- We performed a meta-analysis of reconstructed individual patients survival data from Kaplan–Meier curves of Phase III randomized controlled trials assessing sorafenib as first-line therapy in intermediate/advanced HCC.
- We showed that the median overall survival (10.0 months) and the median time to radiological progression (4.1 months) pooled actuarial probability are extremely variable. No single clinical or tumor characteristic can fully explain this heterogeneity.
- Absence of macrovascular invasion and extra-hepatic disease and HCV etiology are associated with a higher likelihood of survival.
- HCC patients with etiology other than HCV should early shift to second-line therapies.
- Presence of macrovascular invasion and extra-hepatic disease are significant predictors of tumor progression.
- Our pooled actuarial overall survival and time to radiological progression probabilities provide a useful benchmark to indirectly compare the benefit of new first-line agents for advanced HCC, and to better define the correct sequential treatment with second-line agents after failure of sorafenib.

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