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Survival Trends in Sorafenib for Advanced Hepatocellular Carcinoma: A Reconstructed Individual Patient Data Meta-Analysis of Randomized Trials

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Keywords
Hepatocellular carcinoma · Liver cancer · Systemic therapy

Abstract

Background: Emerging data suggest that outcomes for advanced hepatocellular carcinoma (HCC) treated with sorafenib may have improved over time. We aimed to provide robust, time-to-event estimates of survival outcomes for sorafenib in advanced HCC. ***Summary:*** In this systematic review and individual patient data meta-analysis of randomized-controlled trials (RCTs), we searched MEDLINE and Embase from inception till September 2022 for RCTs that provided data for overall survival (OS) and progression-free survival (PFS) for sorafenib monotherapy as first-line systemic therapy for advanced HCC. We performed a pooled analysis using reconstructed individual participant data from published Kaplan-Meier curves to obtain robust estimates for OS and PFS. Of 1,599 articles identified, 29 studies (5,525 patients) met the inclusion criteria. Overall, the median OS was 10.4 (95% CI: 9.6–11.4) months. Median OS increased over time, from 9.8 (95% CI: 8.8–10.7) months in studies before 2015 to 13.4 (95% CI: 11.03–15.24) months in studies from 2015 onwards ($p < 0.001$). OS did not differ by trial phase, geographical region, or study design. The overall median PFS was 4.4 (95% CI: 3.9–4.8) months, but PFS did not improve over time. Sensitivity analysis of studies from 2015 and onwards to account for the introduction of direct-acting antivirals determined that hepatitis C virus

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was associated with reduced mortality ($p < 0.001$). There was minimal heterogeneity in the estimates for OS (all $I^2 \leq 33$). ***Key Messages:*** Survival outcomes for sorafenib in advanced HCC have improved over time. These data have important implications for clinical trial design.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths globally [1]. Despite improvements in cancer surveillance and diagnosis [2, 3], the majority of patients present with advanced disease [4–6]. Sorafenib was the first systemic therapy approved by the US Food and Drug Administration (FDA) for the treatment of advanced HCC [7, 8]. However, sorafenib therapy is limited by modest efficacy, with a median survival of 10.7 months in the landmark SHARP trial [7, 9]. Recent studies including the IMbrave150 and HIMALAYA trials have demonstrated superior survival outcomes in patients receiving immune checkpoint inhibitors compared to sorafenib [10–13].

Despite these recent advancements, sorafenib remains the standard control arm for ongoing randomized trials in advanced HCC. Better medical care, increasing availability of 2nd-line systemic therapy options, as well as safe and effective antivirals for hepatitis C virus (HCV) and hepatitis B virus (HBV), may have contributed to improved survival of patients with advanced HCC [11, 14–18]. Any improvement in the survival of patients receiving sorafenib for advanced HCC may have important implications for clinical trial design as sorafenib is typically used as the comparator in trials of novel therapeutic agents [19–21].

An individual patient data meta-analysis is the gold standard approach for pooled analysis of time-to-event data as it accounts for censoring to assess longitudinal outcomes [22–25]. This allows for accurate estimates of survival outcomes including median survival and percentage survival at specified time points, which could not be estimated by previous conventional meta-analyses. Therefore, we conducted an updated individual patient data meta-analysis using reconstructed individual participant data from randomized-controlled trials (RCTs) to determine the trends in survival outcomes and factors associated with survival among patients receiving sorafenib as first-line systemic therapy for advanced HCC.

Methods

Search Strategy

The synthesis of the literature was performed with reference to the PRISMA for Individual Patient Data (PRISMA-IPD) systematic review guidelines [26, 27]. MEDLINE and Embase databases were searched for relevant articles containing the keywords or MeSH terms relating to "Hepatocellular Carcinoma" and "Sorafenib". The search date was from the inception of databases to the 5th of September 2022. The full search strategy is included in online supplementary Material 1 (see online suppl. material at www.karger.com/doi/10.1159/000529824). All references were imported into Endnote X9 for the removal of duplicates. Manual screening of the references in the included articles was also conducted for a more comprehensive search.

Study Selection and Data Extraction

Four authors (D.J.H.T., A.S.P.T., W.H.L., C.H.N.) independently screened titles and abstracts and subsequently performed a full-text review. Disputes were resolved through consensus from a senior author (D.Q.H.). The primary objective was to evaluate time trends in the overall survival (OS) of patients with advanced HCC treated with sorafenib monotherapy as first-line systemic therapy. The secondary outcomes were to determine time trends in progression-free survival (PFS) and factors associated with OS and PFS. We included phase 2 to 4 RCTs of adult patients (aged ≥18 years) with advanced HCC receiving sorafenib as first-line systemic therapy, either as the treatment or control arm. Only studies that provided Kaplan-Meier plots for OS and/or PFS were included in the analysis as published survival curves were required for the reconstruction of individual participant data. Studies that involved patients receiving sorafenib as part of combination, adjuvant or neoadjuvant therapy with locoregional, surgical, or additional systemic therapy, and studies where patients received sorafenib as a second-line systemic treatment were excluded from the analysis. Studies that compared survival outcomes of sorafenib versus locoregional treatments were also excluded. Where multiple studies provided data for the same cohort, the more updated dataset was included in the final analysis. Relevant data from each included article, including study characteristics and patient demographics, were extracted by a pair of independent authors on a standardized data collection form. Study characteristics included the study start date and date of completion, the number of enrolled patients, the trial phase, and the geographical region according to the World Health Organization (WHO) classification. Patient demographics included mean patient age, patient sex, primary aetiology of liver disease, Eastern Cooperative Oncology Group (ECOG) performance status, Barcelona Clinic Liver Cancer (BCLC) stage, Child-Pugh class, and vascular invasion status.

Statistical Analysis

We reconstructed individual patient time-to-event data from published Kaplan-Meier curves in the included studies using the validated algorithms by Guyot et al. [28]. Digitized images of the published survival curves were processed to obtain their step function values and timings of the steps. Where available, the number-at-risk tables and the total number of events were also used to improve the calibration of time-to-event values. Individual patient survival data were then calculated by solving for the inverted Kaplan-Meier product-limit equations [28]. The

reconstruction of individual patient data is preferred for survival analysis compared to conventional meta-analysis as it accounts for censored observations, provides more accurate estimates of percentage survival at specified time points, and allows for additional calculations, including median survival time [28–33].

Following the reconstruction of individual patient data, pooled analysis was conducted using the *MetaSurv* methodology in which arcsine-transformed survival probabilities were aggregated using a random-effects model to obtain a distribution-free summary survival curve [34–36]. This provides robust estimates for the median OS and OS at specified time points of 3, 6, and 9 months and 1 and 2 years. A similar analysis was conducted to obtain pooled estimates for the secondary outcome of PFS. Between-study heterogeneity was assessed via I^2 values, where an I^2 value of <50%, 50–75%, and >75% represented low, moderate, and high degrees of heterogeneity, respectively [37, 38]. In order to further investigate possible sources of between-study heterogeneity, prespecified subgroup analyses were conducted based on time period of the studies (start date of trial before 2015 vs. 2015 and after), phase of the clinical trial (phase 2 vs. 3), and geographical location. Between-strata comparisons were conducted via the formulas detailed in the *MetaSurv* methodology [36]. Additionally, we performed regression analysis using a generalized linear model with a log link function to investigate the effect of patient demographics, including age, sex, aetiology of liver disease, ECOG performance status, BCLC stage, Child-Pugh class, vascular invasion status, and previous locoregional therapy, on the survival outcomes of patients with advanced HCC receiving sorafenib in person-years. The coefficients were then exponentiated to obtain beta coefficients and their corresponding standard errors (SE). All statistical analyses were conducted in R studio (ver. 4.0.3) and a p value <0.05 was considered as the threshold for statistical significance.

Quality Assessment and Risk of Bias

The quality of included articles was evaluated using the Cochrane Risk-of-Bias 2 tool [39], which evaluates studies on the domains of the robustness of the randomization process, deviation from the intended interventions, completeness of outcome data, measurement of outcomes, and selection of the reported results. Funnel plots were constructed for analyses involving more than ten studies, and publication bias was assessed via visual inspection of funnel plots for asymmetrical distribution of the data points across the vertical treatment effect axis [40].

Results

Summary of Included Articles

The initial search yielded 1,599 articles. After the removal of 320 duplicates through the title and abstract sieve, 290 articles were retrieved for full-text review. A final 29 studies from 2008 to 2022 were included in this meta-analysis (Fig. 1). Eight studies were conducted in the Western Pacific region [41–48], six studies in Europe region [49–54], two studies in the Americas [55, 56], and one study in Africa [57]. A total of 12 studies were multinational studies [7, 13, 58–67]. Overall, 5,525 patients with advanced HCC were randomized to the sorafenib arm in the RCTs included in this meta-analysis. A summary of the included articles is included in online supplementary Material 2. All included studies had a low risk of bias according to the Cochrane Risk-of-Bias 2 assessment tool (online suppl. Material 3).

OS of Patients with Advanced HCC Receiving Sorafenib

From a pooled analysis of 29 studies and 5,525 patients with advanced HCC receiving sorafenib, the median OS was 10.43 (95% CI: 9.59–11.38) months (Fig. 2; online suppl. Material 4). OS was 88.8% (95% CI: 86.5–91.2%) at 3 months, 70.0% (95% CI: 67.0–73.2%) at 6 months, 45.0% (95% CI: 41.6–48.5%) at 1 year, and 20.4% (95% CI: 17.3–24.0%) at 2 years (Table 1).

Trends in Survival

Prespecified subgroup analysis was conducted based on the study enrolment date. In studies with a start date before 2015, the median OS of patients with advanced HCC receiving sorafenib was 9.78 (95% CI: 8.79–10.73) months (23 studies, 3,860 patients), significantly lower than the median OS in studies with enrolment dates in 2015 and onwards (median OS: 13.38 months, 95% CI: 11.03–15.24; 6 studies, 1,665 patients) ($p < 0.001$) (Fig. 3).

We performed a secondary analysis comparing different time periods. In studies with a start date before 2010, the median OS of patients with advanced HCC receiving sorafenib was 9.40 months (95% CI: 8.20–10.66 months) (9 studies, 2,086 patients) (23 studies, 3,860 patients), significantly poorer than studies with enrolment dates in 2010 and onwards (median OS: 11.03 months, 95% CI: 9.98–12.35 months) (20 studies, 3,439 patients) ($p < 0.001$).

Trial Phase

The median OS in phase 2 trials was 9.94 months (95% CI: 8.08–11.35 months) (13 studies, 579 patients), and 10.73 months (95% CI: 9.73–12.04 months) in phase 3 trials, with no significant difference based on trial phase ($p = 0.126$).

Geographical Region

The pooled median OS of patients with advanced HCC receiving sorafenib was 9.31 months (95% CI: 7.45–10.31 months) in studies conducted only in the Americas (2 studies, 176 patients), 7.51 months (95% CI: 5.45–11.25 months) in studies conducted in Europe (6 studies, 313 patients), and 9.61 months (95% CI: 7.54–11.60 months) in studies conducted in the Western Pacific (8 studies, 930

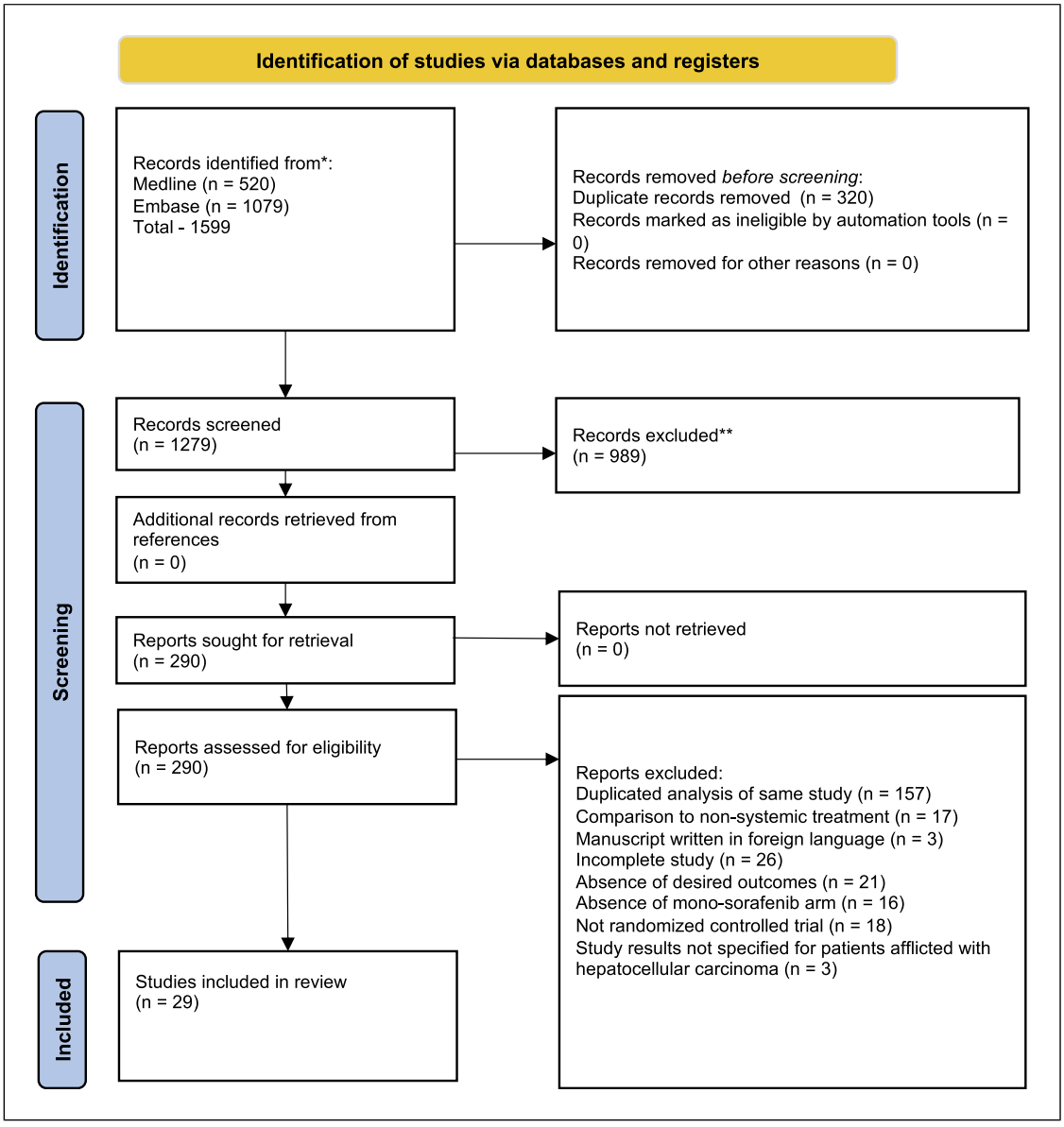

Fig. 1. PRISMA flow chart of included articles.

patients). Only one study was conducted in Africa, hence precluding pooled analysis. There was no significant difference in OS based on geographical location (p = 0.496).

Study Design

In multicentre trials, the median OS was 11.69 (95% CI: 10.43–12.90) months (12 studies, 4,025 patients), compared to 9.13 (95% CI: 7.72–10.55) months in single-centre trials (17 studies, 1,500 patients) (p = 0.055).

Factors Associated with Mortality

Overall Analysis

In meta-regression, the risk of mortality was found to decrease over time (β: 0.97, SE: 0.01, p = 0.013) (Table 2) and with Child-Pugh A cirrhosis (β: 0.39, SE: 0.04, p < 0.001). However, Child-Pugh B cirrhosis (β: 2.58, SE: 0.28, p < 0.001), presence of macrovascular invasion (β: 3.49, SE: 1.57, p = 0.007), and alcohol-associated HCC (β: 2.29, SE: 0.45, p = 0.001) were associated with higher mortality. Study-level data for age, sex, ECOG performance status, HBV, HCV, BCLC stage, and

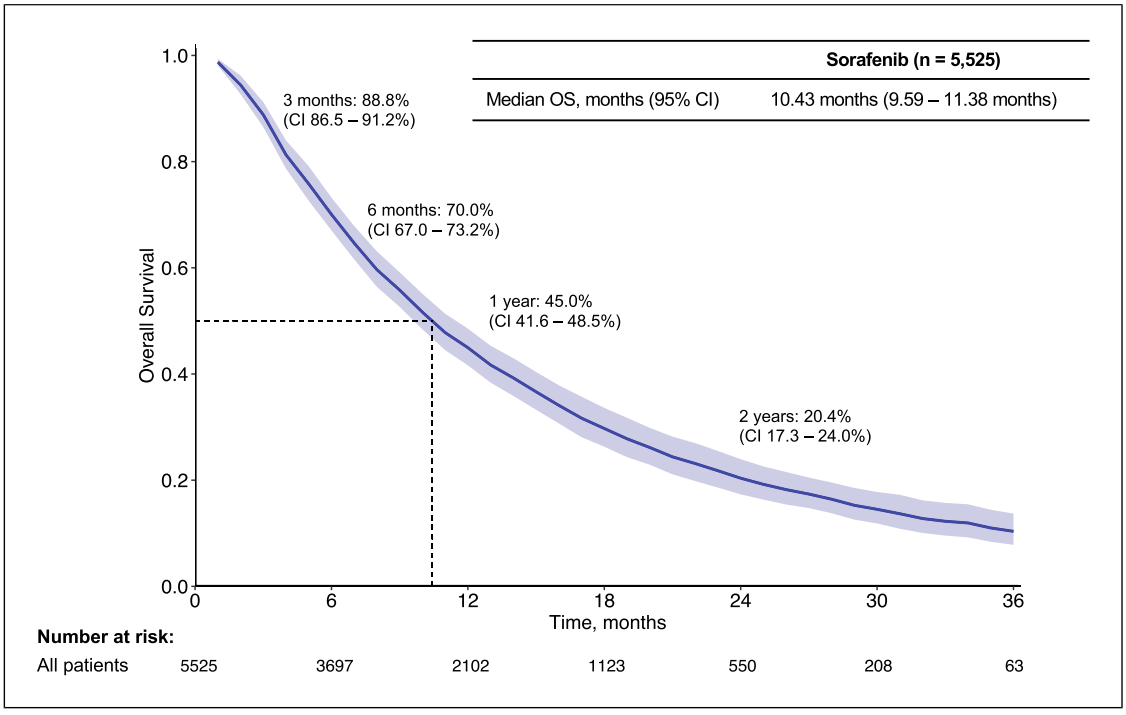

Fig. 2. OS of patients with advanced HCC receiving sorafenib.

previous locoregional therapy were not significantly associated with increased mortality.

Sensitivity Analysis for Studies from 2015 and Beyond

Prespecified sensitivity analysis was conducted for studies with enrolment dates from 2015 and onwards as direct-acting antivirals (DAAs) for HCV were introduced during this time frame. HCV (β: 0.31, SE: 0.03, $p < 0.001$) and ECOG performance status 0 (β: 0.38, SE: 0.09, $p = 0.023$) were associated with a lower risk of mortality. Study-level data for age, sex, BCLC stage, other aetiologies of liver disease including HBV and non-viral HCC, and previous locoregional therapy were not associated with increased mortality.

PFS of Patients with Advanced HCC Treated with Sorafenib

From an analysis of 27 studies and 5,139 patients, the median PFS was 4.42 months (95% CI: 3.92–4.84 months). PFS was 98.0% (95% CI: 96.8–99.2%) at 1 month, 62.0 (95% CI: 56.4–68.2%) at 3 months, 37.4 (95% CI: 33.1–42.3%) at 6 months, and 18.1% (95% CI: 15.3–21.4%) at 1 year (Table 3).

Trends in Survival

Subgroup analysis was conducted for PFS according to the study enrolment date. There was no significant difference in PFS between studies with start dates before 2015 (median PFS: 4.40, 95% CI: 3.75–4.91 months; 22 studies, 3,805 patients) versus studies with start dates in 2015 and beyond (median PFS: 4.32 months, 95% CI: 3.26–5.15 months; 5 studies, 1,334 patients) ($p = 0.123$).

Trial Phase

The median PFS in phase 2 trials was 4.21 months (95% CI: 3.25–5.15 months), which was similar to the median PFS in phase 3 trials (median PFS: 4.31 months, 95% CI: 3.53–4.84 months) ($p = 0.706$).

Geographical Region

In subgroup analysis for pooled median PFS by geographical region, the median PFS was highest in studies conducted in Europe (5.16 months, 95% CI: 4.14–6.49 months), followed by the Americas (4.53 months, 95% CI: 3.79–5.29 months), and lowest in studies conducted in the Western Pacific (3.25 months, 2.77–3.96 months) ($p < 0.001$).

Study Design

The median PFS was higher in multicentre RCTs (4.53 months, 95% CI: 4.09–4.97) versus single-centre trials (4.06 months, 95% CI: 2.98–4.80) in single-centre trials ($p < 0.001$).

Table 1. Summary of OS for sorafenib in advanced HCC

OS	Studies, *n*	Patients, *N*	Median OS (months)	3-Month OS (%)	6-Month OS (%)	1-Year OS (%)	2-Year OS (%)	*p* value*	I^2
Overall	29	5,525	14.30 (9.59–11.38)	88.8 (86.5–91.2)	70.0 (67.0–73.2)	45.0 (41.6–48.5)	20.4 (17.3–24.0)		7.60
Time period								<**0.001**	
Before 2015	23	3,860	9.78 (8.79–10.73)	87.7 (85.2–90.3)	67.8 (64.0–71.8)	42.3 (38.5–46.3)	17.9 (14.8–21.6)		5.10
2015 and after	6	1,665	13.38 (11.03–15.24)	91.0 (88.5–93.7)	75.9 (72.8–79.2)	53.7 (48.9–58.8)	28.1 (22.6–35.1)		0.00
Trial phase								0.126	
Phase 2	13	579	9.94 (8.08–11.35)	88.3 (83.7–93.2)	70.0 (63.1–77.7)	42.0 (36.3–48.6)	14.7 (10.5–20.6)		0.00
Phase 3	16	4,946	17.30 (9.73–12.04)	89.3 (87.6–91.0)	70.5 (67.2–73.9)	46.3 (42.6–50.3)	22.4 (19.3–26.1)		33.20
Geographical region								0.496	
Americas	2	219	9.31 (7.45–131)	89.5 (79.1–100.0)	67.4 (60.9–74.6)	37.6 (31.3–45.2)	11.4 (6.4–20.2)		0.00
Europe	6	313	7.51 (5.45–11.25)	84.8 (75.5–95.1)	60.2 (46.4–78.0)	37.0 (27.0–50.9)	12.4 (6.8–22.5)		0.00
Western Pacific	8	930	9.61 (7.54–11.60)	88.3 (84.5–92.2)	69.3 (60.5–79.4)	40.4 (32.3–50.4)	13.5 (7.7–23.7)		0.00
Multicentre trial								0.496	
Yes	12	4,025	11.69 (10.43–12.90)	89.9 (88.0–91.9)	73.1 (70.0–76.3)	49.1 (45.4–53.3)	24.6 (21.0–28.9)		23.70
No	17	1,500	9.13 (7.72–10.55)	87.8 (83.7–92.0)	66.6 (60.7–73.1)	40.1 (34.9–46.1)	14.5 (10.8–19.4)		0.00

A *p* value <0.05 was considered to be statistically significant. OS, overall survival. **p* value refers to subgroup difference for OS between prespecified subgroups.

Heterogeneity and Publication Bias

There was a low degree of heterogeneity in the overall analysis for OS and in all subgroup analyses for OS (all $I^2 \leq 33$). Moderate heterogeneity was found in the overall analysis for PFS, and in the subgroup analysis of PFS in trials with enrolment dates before 2015, in phase 3 trials, in trials conducted in the Western Pacific region, and in multicentre studies. From the visual assessment of funnel plots, there was no significant publication bias in the overall analyses for OS and PFS in patients with advanced HCC receiving sorafenib.

Discussion

Main Findings

In this large systematic review and meta-analysis of 29 RCTs and 5,525 individuals, we reconstructed individual participant data to provide robust survival estimates for sorafenib monotherapy as a first-line systemic therapy for advanced HCC. We determined that the overall median OS was 10.4 months. However, the median OS improved from 9.8 months in studies before 2015 to 13.4 months in studies from 2015 and beyond. There was a similar improvement in survival when comparing studies before 2010 with studies conducted from 2010 and beyond. There were no significant differences in OS by trial phase, design, or region and no significant improvement in PFS over time. In meta-regression analysis of all included studies, survival improved over time, while Child-Pugh class B, macrovascular invasion, and alcohol were associated with poorer survival. HCV was not associated with improved survival in the overall meta-regression analysis, but prespecified sensitivity analyses for studies conducted from 2015 and beyond determined that the presence of HCV was associated with significant improvement in OS. There was a low degree of heterogeneity in the estimates for OS and all included studies were of high quality.

These data have important implications for clinical trial design. Several recent trials have failed to achieve the primary endpoint of improved OS compared to sorafenib [59, 67]. A contributing factor to the failure of these recent trials was the higher-than-expected median OS of participants that received sorafenib. The reconstructed individual participant data in our study

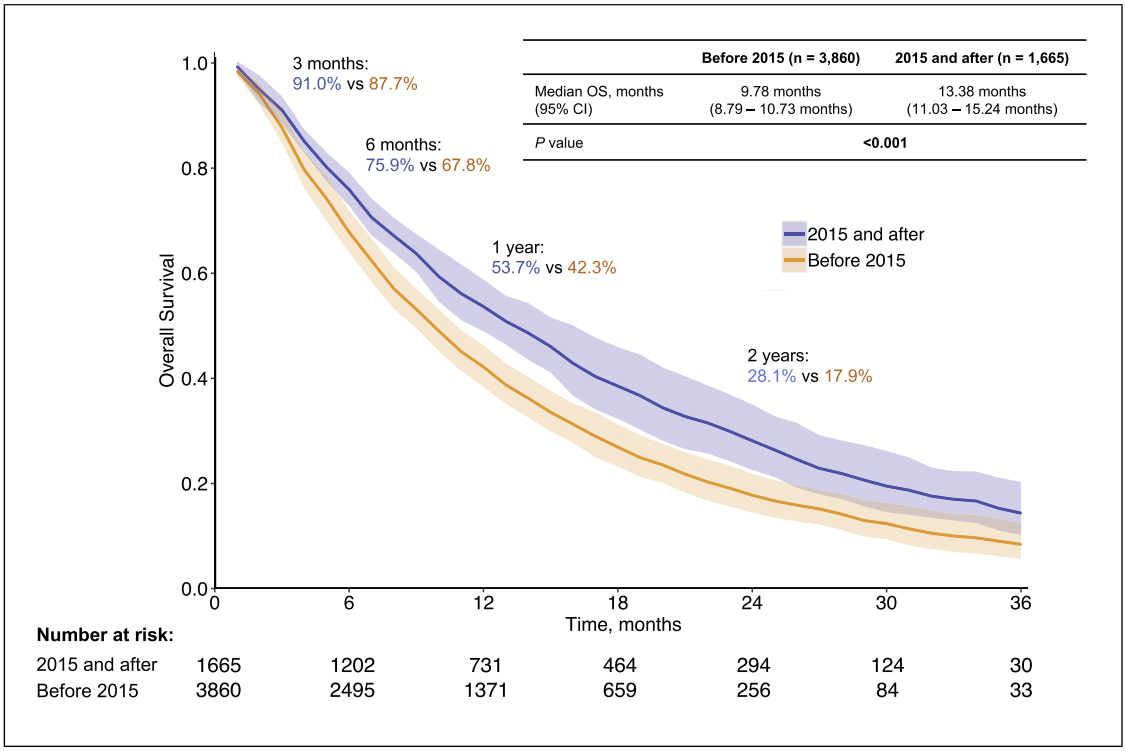

Fig. 3. OS of patients with advanced HCC receiving sorafenib, comparing studies with enrolment dates before 2015 versus 2015 and beyond.

provides strong evidence that the survival of patients receiving first-line sorafenib monotherapy has improved over time, although the absolute difference of 3.6 months in studies before 2015 versus those from 2015 and beyond was modest. These data may influence sample size calculations for future trials. The improvement in survival over time is likely multifactorial and possibly related to the availability of second-line systemic therapies, better medical care, and the increasing availability of effective antiviral therapies for viral-associated HCC [11, 68, 69]. Meta-regression for RCTs after 2015 determined that the presence of HCV was the only study-level factor that was associated with improved survival, coinciding with the availability of DAAs for HCV, although previous trials did not require antiviral therapy for HCV as an inclusion criteria [12, 65, 67]. The effect of HCV on improved survival outcomes has been previously reported in individual patient meta-analyses of phase 3 trials [70, 71], with recent studies also suggesting that HCV is associated with reduced rates of tumour growth compared to other aetiologies in patients receiving sorafenib [72]. While sorafenib may have relatively higher efficacy in patients with active HCV viremia, it is unclear if these reported benefits extend to patients with treated HCV. The exact mechanisms by which HCV possibly enhances tumour response to sorafenib remain unclear, and survival outcomes of patients with HCV-associated HCC receiving sorafenib have not been the primary endpoint of clinical trials. It therefore remains important to continue tracking data for aetiology and antiviral treatment status in clinical trials to define subgroups of patients who may have differing survival with systemic therapy [13, 73].

Differences in PFS by geographical region were observed, with longer median PFS in studies conducted in Europe (5.2 months) and the Americas (4.5 months) compared to the Western Pacific region (3.3 months). This could be related to differences in the predominant aetiology of liver disease, with a greater proportion of HCV-associated HCC in Europe and the Americas compared to the Western Pacific where HBV is the leading cause of HCC [16]. Enhanced tumour response to sorafenib in HCV-associated HCC may have contributed to longer PFS in the former regions [72]. However, additional confounding factors including antiviral treatment status and previous locoregional treatment could not be accounted for in this analysis and these results require validation.

Table 2. Meta-regression of factors associated with mortality, overall and sensitivity analysis for studies with enrolment dates from 2015 and beyond

Variable	Studies	Patients	β coefficient	SE	*p* value
All studies					
Time (years)	29	5,525	0.968	0.012	**0.013**
Age (years)	28	5,167	1.010	0.017	0.556
Male (%)	27	5,265	3.888	5.226	0.149
Aetiology, (%)					
HBV	24	5,171	0.698	0.254	0.333
HCV	24	5,171	0.681	0.226	0.261
Non-viral	24	5,171	1.376	0.338	0.21
Alcohol	14	2,479	2.291	0.449	**0.001**
Child-Pugh class, (%)					
A	28	5,360	0.386	0.042	<**0.001**
B	28	5,360	2.581	0.279	<**0.001**
ECOG performance status, (%)					
0	24	5,103	0.704	0.149	0.113
1	24	5,103	1.422	0.404	0.228
BCLC stage, (%)					
B	23	4,934	0.426	0.232	0.133
C	23	4,934	2.718	1.397	0.065
Macrovascular invasion (%)	15	3,595	3.487	1.573	**0.007**
Previous LRT (%)	18	3,432	0.733	0.179	0.227
2015 and onwards					
Age (years)	6	1,665	0.982	0.012	0.116
Male %	5	1,448	26.154	57.696	0.236
Aetiology, (%)					
HBV	6	1,665	1.520	0.327	0.064
HCV	6	1,665	0.313	0.030	<**0.001**
Non-viral	6	1,665	0.488	0.247	0.156
Alcohol	–				
Child-Pugh class, (%)					
A	–				
B	–				
ECOG performance status, (%)					
0	5	1,500	0.383	0.085	0.023
1	5	1,500	2.635	0.588	0.025
BCLC stage, (%)					
B	5	1,500	0.210	0.167	0.144
C	5	1,500	5.414	3.492	0.079
Macrovascular invasion (%)	–				
Previous LRT (%)	5	1,500	1.462	0.262	0.124

BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; LRT, locoregional treatment.

Despite the improvement in OS in patients with advanced HCC treated with sorafenib over time, the median OS of 13.4 months for sorafenib in the current analysis for studies after 2015 remains substantially lower than the median OS of 19.2 months reported with atezolizumab plus bevacizumab [60], emphasizing that sorafenib should no longer be considered the standard of care for treatment of patients with advanced HCC. Despite improvements in survival with sorafenib, future trials should utilize ateolizumab plus bevacizumab or other recently approved first-line options as the comparator in place of sorafenib for the benefit of participants randomized to the control arm.

In Context with Current Literature

Brown and colleagues previously reported survival outcomes for sorafenib in advanced HCC; however, the study by Brown utilized conventional meta-analysis methodology, did not account for censoring, and did not address heterogeneity [19]. In addition, multiple large studies have been published since the study by Brown and colleagues, with the current study including data from 13

Table 3. PFS for sorafenib in advanced HCC

OS	Studies, *n*	Patients, *N*	Median PFS (months)	3-Month PFS (%)	6-Month PFS (%)	9-Month PFS (%)	1-Year PFS (%)	*p* value*	I^2
Overall	27	5,139	4.42 (3.92–4.84)	62.0 (56.4–68.2)	37.4 (33.1–42.3)	25.7 (22.3–29.7)	18.1 (15.3–21.4)		51.20
Time period								0.123	
Before 2015	22	3,805	4.40 (3.75–4.91)	62.5 (55.6–70.2)	37.4 (32.1–43.6)	25.7 (21.5–30.8)	18.4 (12.0–23.3)		52.20
2015 and after	5	1,334	4.32 (3.26–5.15)	59.4 (52.2–67.5)	36.4 (29.4–45.0)	25.2 (19.4–32.7)	16.7 (12.0–23.3)		47.00
Trial phase								0.706	
Phase 2	12	524	4.21 (3.25–5.15)	62.7 (53.4–73.7)	35.1 (26.2–47.0)	24.9 (17.2–36.0)	18.4 (11.7–28.9)		3.10
Phase 3	15	4,615	4.31 (3.53–4.84)	60.6 (53.4–68.8)	36.3 (31.1–42.5)	24.2 (20.4–28.6)	16.5 (13.7–20.0)		63.70
Geographical region								<**0.001**	
Americas	2	219	4.53 (3.79–5.29)	66.1 (59.4–73.5)	37.4 (30.8–45.6)	29.6 (23.4–37.4)	23.4 (17.7–30.8)		33.40
Europe	6	313	5.16 (4.14–6.49)	83.1 (78.8–87.7)	46.0 (39.8–53.2)	30.4 (24.7–37.4)	23.2 (18.0–29.9)		48.00
Western Pacific	7	599	3.25 (2.77–3.96)	51.9 (46.8–57.4)	24.7 (20.2–30.2)	15.5 (11.7–20.5)	9.6 (6.4–14.2)		35.60
Multicentre trial								<**0.001**	
Yes	11	3,970	4.53 (4.09–4.97)	60.0 (55.9–64.5)	39.4 (35.5–43.8)	27.7 (24.2–31.7)	19.1 (16.6–22.1)		59.10
No	16	1,169	4.06 (2.98–4.80)	61.8 (50.9–75.0)	31.8 (23.5–43.0)	21.3 (15.0–30.2)	15.2 (10.0–23.1)		33.80

A p value <0.05 was considered to be statistically significant. PFS, progression-free survival. *p value refers to subgroup difference for OS between prespecified subgroups.

additional RCTs [13, 59, 67]. The current study provides updated, robust, time-to-event survival estimates with minimal heterogeneity and extensive subgroup analyses.

Strengths and Limitations

The current study is the first meta-analysis in this area to utilize reconstructed individual participant data meta-analysis, which is considered to be the gold standard for reporting survival data as it accounts for the censoring of events [74]. There was minimal heterogeneity in the estimates for OS, and all included studies were of high quality. These data are useful as they provide robust, pooled estimates of survival with minimal heterogeneity that may be utilized in sample-size calculations for clinical trials. However, this study is not without limitations. Only RCTs were included in the analysis, which have selective inclusion criteria for patient enrolment and protocols for discontinuation. Therefore, these findings require further validation in real-world clinical practice. There were also insufficient data to determine the antiviral treatment status among patients with HCV, emphasizing the importance of collecting granular data for aetiology in future trials.

Conclusions

This reconstructed individual patient data meta-analysis of RCTs provides high-level evidence that survival with sorafenib as first-line systemic therapy for HCC has improved over time. These data have important implications for clinical trial design.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

AV reports personal fees from Roche, Bayer, Bristol Myers Squibb, Lilly, EISAI, AstraZeneca, Ipsen, Merck Sharp and Dohme,

Sirtex, BTG, Servier, Terumo, and Imaging Equipment (Advanced Accelerator Applications). TY reports consulting fees from, honoraria from, and participation on a data safety monitoring board or advisory board for AbbVie, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Eli Lilly, EMD Serono, Exelixis, H3 Biomedicine, Ipsen, Merck Sharp and Dohme, New B Innovation, Novartis, OrigiMed, Pfizer, Sillajen, Sirtex, and Taiho Pharmaceutical.

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Author Contributions

All authors approve the final version of the manuscript, including the authorship list, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Conceptualization: D.Q.H. and R.L. Data curation: D.J.H.T., A.S.P.T., W.H.L., and C.H.N. Formal analysis: D.J.H.T., A.S.P.T., and W.H.L. Supervision: D.Q.H. Validation: C.F., J.X., B.K., and P.W.L.T. Writing – original draft: D.J.H.T., A.S.P.T., W.H.L., C.H.N., and D.Q.H. Writing, review, and editing: D.J.H.T., A.S.P.T., W.H.L., C.H.N., C.F., B.N., J.X., B.K., P.W.L.T., E.X.T., M.T., N.S., M.D.M., N.T., S.W.L., B.K.K., T.Y., A.V., R.L., and D.Q.H. All authors have read and approved the final version of the manuscript for submission.

Data Availability Statement

All articles included in the analysis conducted in this manuscript are available from MEDLINE and Embase. All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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