VOLUME 35 · NUMBER 6 · FEBRUARY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Impact of Viral Status on Survival in Patients Receiving Sorafenib for Advanced Hepatocellular Cancer: A Meta-Analysis of Randomized Phase III Trials

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Published at ascopubs.org/journal/jco on January 3, 2017.

This study was published in abstract form in the proceedings of the International Liver Congress 2016 in Barcelona, Spain.

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0732-183X/17/3506w-622w/$20.00

## ABSTRACT

### Purpose

Following the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, sorafenib has become the standard of care for patients with advanced unresectable hepatocellular carcinoma, but the relation between survival advantage and disease etiology remains unclear. To address this, we undertook an individual patient data meta-analysis of three large prospective randomized trials in which sorafenib was the control arm.

### Methods

Of a total of 3,256 patients, 1,643 (50%) who received sorafenib were available. The primary end point was overall survival (OS). A Bayesian hierarchical approach for individual patient data meta-analyses was applied using a piecewise exponential model. Results are presented in terms of hazard ratios comparing sorafenib with alternative therapies according to hepatitis C virus (HCV) or hepatitis B virus (HBV) status.

### Results

Hazard ratios show improved OS for sorafenib in patients who are both HBV negative and HCV positive (log [hazard ratio], −0.27; 95% CI, −0.46 to −0.06). Median unadjusted survival is 12.6 (11.15 to 13.8) months for sorafenib and 10.2 (8.88 to 12.2) months for "other" treatments in this subgroup. There was no evidence of improvement in OS for any other patient subgroups defined by HBV and HCV. Results were consistent across all trials with heterogeneity assessed using Cochran's Q statistic.

### Conclusion

There is consistent evidence that the effect of sorafenib on OS is dependent on patients' hepatitis status. There is an improved OS for patients negative for HBV and positive for HCV when treated with sorafenib. There was no evidence of any improvement in OS attributable to sorafenib for patients positive for HBV and negative for HCV.

*J Clin Oncol 35:622-628. © 2017 by American Society of Clinical Oncology*

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer and the third leading cause of cancer deaths worldwide, with more than 500,000 people affected each year.[1,2]

The development of HCC has well-established causal links to chronic viral hepatitis types B (HBV) and C (HCV) and the other causes of chronic liver disease.[1,2] In the absence of a rigorous surveillance program, most patients with HCC are not suitable for potentially curative treatments such as surgical resection, due to the advanced stage of the disease at presentation.[3]

The current standard of care for advanced unresectable HCC (aHCC) is sorafenib. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, which involved this multikinase inhibitor, was the first prospective, randomized, placebo-controlled trial to show survival benefit for patients with aHCC, although this benefit was modest (median survival, 10.7 months with sorafenib *v* 7.9 months with placebo).[4] Similar results were subsequently reported from the Asia-Pacific study, although the absolute survival figures were lower.[5] The difference in these two trials might be related to ethnicity or differences in underlying liver function related to the intensity of treatment before trial entry.

ASSOCIATED CONTENT

Appendix
DOI: 10.1200/JCO.2016.69.5197

DOI: 10.1200/JCO.2016.69.5197

In an exploratory subgroup analysis of the SHARP trial, there was an increased survival attributable to sorafenib in patients who were HCV positive (median survival, 14 *v* 7.4 months).[6] Because sorafenib was subsequently shown to have little or no effect on HCV viral load,[7] this observation was not pursued.

Three large, two-armed, noninferiority, phase III multicenter, randomized controlled trials (RCTs) have investigated the use of other targeted agents, namely, brivanib,[8] sunitinib,[9] and linifanib,[10] all including sorafenib as the control arm. An aggregate meta-analysis[11] suggested that sorafenib might be more efficacious in patients positive for HCV. Other authors[12-14] have considered the hypothesis that etiologic factors (such as HCV positivity) might be predictive of better response to sorafenib, and discussed possible mechanisms.

In this study, we undertook an individual patient data (IPD) meta-analysis of phase III RCTs that used sorafenib as a control arm, with the aim of investigating the effect of etiology, defined by patients' HBV and HCV status, on overall survival (OS). IPD meta-analyses have a major advantage over aggregate meta-analyses in that they ensure consistent analytic techniques and allow for detailed inspection of interaction or subgroup effects that are not available in published evidence.[15,16]

## METHODS

### Data Collection

Data were taken from three phase III clinical trials that included sorafenib as a control arm.[8-10] IPD from the brivanib and sunitinib trials were available in their entirety. IPD from the linifanib trial were accessed by a remote system made available by the study sponsor, and aggregate data were extracted from equivalent models. IPD from the brivanib and sunitinib trials and aggregate data from the linifanib trial were combined and included in the full meta-analysis.

Data on OS as well as previously identified key prognostic factors of interest, including Eastern Cooperative Oncology Group (ECOG) status, extrahepatic spread, local invasion, serum biomarker alpha-fetoprotein (AFP), HBV status, HCV status, and treatment, were collected.

### Study Quality

The protocols of each study were reviewed to assess suitability of comparisons. Registration numbers for the brivanib,[8] sunitinib,[9] and linifanib[10] trials were NCT00858871, NCT006993749, and NCT01009593, respectively. All three studies were similar in terms of their overall design, patient groups, inclusion and exclusion criteria, methods of diagnosis, and assessment (Appendix Table A1, online only).

### Statistical Methodology

All analyses were carried out on the intention-to-treat principle, retaining patients in their initial treatment groups irrespective of any protocol violations. The primary outcome of interest was OS measured as the time from random assignment until death from any cause. Survival estimates from each study were calculated using the Kaplan-Meier method, with median follow-up calculated using the reverse Kaplan-Meier method.[17] Multivariable analyses within each study were carried out using Cox proportional hazards models.

Meta-analyses on IPD were carried out using a hierarchical Bayesian model.[16,18] Data were analyzed using proportional hazards methods with a piecewise exponential model[19] used to model the baseline hazard function. Treatment comparisons and comparisons of other patient subgroups were evaluated using hazard ratios (HRs).

Models were fitted using uninformative prior distributions taking the form of normal distributions with a zero mean and large standard deviations (no. 0 to 1,000) for all log HRs and the log HRs of the piecewise exponential model. Parameter estimates were obtained from 10,000 draws from multiple chains after convergence had been confirmed. A thin of 5 was used to account for observed auto-correlation. Results are presented in the form of forest plots, with parameter estimates presented in terms of posterior medians and associated 95% credibility intervals.

The aim of the analysis was to evaluate the use of sorafenib as the standard of care against alternative therapies ("other") within patient etiologic subgroups. Here brivanib, sunitinib, and linifanib were analyzed as a single "other" group, with the intention of demonstrating consistency of results across the three sources of data and of evaluating the use of sorafenib. The main comparisons of interest were the HRs comparing sorafenib with other alternative therapies in each etiologic subgroup. Here, the key efficacy parameters are a hierarchical term that assumed the treatment effect comparing sorafenib with alternative therapies is not fixed but is drawn from some distribution of treatment effects and acknowledges that the alternative therapy differs between trials included in the meta-analysis.

Models were constructed, adjusting for known key prognostic factors of interest—extrahepatic spread, local invasion, ECOG status, AFP status, HBV and HCV status—as main effects. The main question of interest was whether the effect of treatment differs according to patient etiology. All four levels formed by the interaction between HBV and HCV were considered with models fitted, which include HRs comparing sorafenib with alternative therapies as nested terms within each etiology status. Here, treatment effects were estimated for each subgroup of patients depending on their hepatitis status. The comparisons of HRs from different sources were evaluated using the Cochran Q statistic[20] to assess for model heterogeneity.

Sensitivity analyses were carried out that compared sorafenib against other treatments as a two-stage meta-analysis by extracting the applicable HRs from each trial individually and comparing them using a traditional aggregate meta-analysis approach. Further sensitivity analyses were carried out comparing sorafenib with other therapies without adjusting for other key prognostic factors.

Toxicity data were assessed across trials in an aggregate fashion in terms of the number of grade 3/4 events recorded. Comparisons between sorafenib and alternative therapies are presented in terms of the relative risk and were compared across studies using a standard aggregate meta-analytical approach. Analyses considered the total number of grade 3/4 events across trials, with heterogeneity assessed using the $I^2$ statistic.

IPD models were fitted using the statistical package WinBUGS with data manipulation, production of tables and figures, and the analyses of toxicity data all produced using the statistical package R. Remotely accessed data from the linifanib trial were evaluated using SAS Clinical Trial Data Transparency (version 4.5; SAS Institute, Cary, NC) system. All analyses were carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

## RESULTS

### Patient Characteristics

Data on 3,256 patients were collected from the three phase III clinical trials (brivanib trial, n = 1,155 [36%][8]; sunitinib trial, n = 1,070 [32%][9]; linifanib trial, n = 1,031 [32%]).[10] Overall, 1,643 patients (50%) received sorafenib, 577 (18%) received brivanib, 526 (16%) received sunitinib, and 510 (16%) received linifanib. Baseline patient characteristics are listed in Table 1. Analyses were carried out on the 2,863 patients (88%) who had both a defined HBV and HCV status and for whom OS data were available.

**Table 1.** Patient Demographics by Trial

| Variable | Study | | | *P* |
|---|---|---|---|---|
| | Johnson et al[8] (N = 1,155) | Cheng et al[9] (N = 1,070) | Cainap et al[10] (N = 1,031) | |
| Arm | | | | N/A |
| Sorafenib | 578 (50) | 544 (50.8) | 521 (50.5) | |
| Brivanib | 577 (50) | N/A | N/A | |
| Sunitinib | N/A | 526 (49.2) | N/A | |
| Linifanib | N/A | N/A | 510 (49.5) | |
| Sex | | | | .528 |
| Female | 188 (16.3) | 179 (16.7) | 155 (15.0) | |
| Male | 967 (83.7) | 891 (83.3) | 876 (85.0) | |
| Age, median (IQR), years | 61 (53-69) | 59 (49-68) | 60 (51-68) | N/A |
| ECOG status | | | | < .001 |
| 0 | 720 (62.3) | 577 (54.1) | 671 (65.1) | |
| 1 | 435 (37.7) | 490 (45.9) | 360 (34.9) | |
| Vascular invasion | | | | < .001 |
| No | 842 (72.9) | 712 (68.1) | 583 (56.5) | |
| Yes | 313 (27.1) | 334 (31.9) | 448 (43.5) | |
| Extrahepatic spread | | | | < .001 |
| No | 433 (37.5) | 715 (66.8) | 430 (41.7) | |
| Yes | 722 (62.5) | 355 (33.2) | 601 (58.3) | |
| AFP, median (IQR), ng/mL | 160 (9.0 to 2,537) | 256 (13 to 4,000) | 389 (17.5 to 8,523) | .111 |
| HBV | | | | < .001 |
| No | 361 (41.4) | 459 (44.3) | 526 (51.0) | |
| Yes | 512 (58.6) | 578 (55.7) | 505 (49.0) | |
| HCV | | | | .101 |
| No | 640 (73.1) | 786 (77.4) | 772 (74.9) | |
| Yes | 235 (26.9) | 230 (22.6) | 259 (25.1) | |

NOTE. Data given as No. (%) unless otherwise indicated.
Abbreviations: AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; N/A, not applicable.

Comparing the key prognostic indicators across trials, there was evidence of different patient distributions according to ECOG status, vascular invasion, extrahepatic spread, and HBV status. Generally, the patient population differed in the sunitinib trial, with a larger proportion of patients with ECOG performance status (PS) of 1 (45.9% *v* 37.7% for brivanib and 34.9% for linifanib) and a smaller proportion of patients with extrahepatic spread (33.2% *v* 62.5% [brivanib] and 58.3% [linifanib]). The linifanib trial had a notably larger proportion of patients with vascular invasion (43.5% *v* 27.1% and 31.9%) and smaller proportion of patients who are hepatitis B positive (49% *v* 58.6% [brivanib] and 55.7% [sunitinib]). The proportion of patients positive for HCV was consistent across all three trials (26.9% [brivanib], 22.6% [sunitinib], and 25.1% [linifanib]).

### *Overall Survival*

Median follow-up was 20.0 months (20.8, 22.2, and 15.9 months in the brivanib, sunitinib, and linifanib trials, respectively). Unadjusted OS estimates from each study are given in Figure 1. Median (95% CI) unadjusted survival estimates were 9.67 (8.78 to 10.65), 8.45 (7.76 to 9.24), and 9.1 (8.2 to 9.92) months for the brivanib, sunitinib, and linifanib trials, respectively.

Exploratory analyses (unpublished) of patients with aHCC identified HBV, HCV, AFP (measured on the log scale), tumor local invasion, extrahepatic spread, and ECOG PS as key prognostic indicators. Figure 2 shows the main effect that each of these had on OS in their respective studies. Local invasion, extrahepatic spread, an ECOG PS of 1 (*v* 0) and an increase in log AFP levels all significantly increased the hazard of observing an event. There was a trend of patients who were HBV positive all having an increased hazard compared with patients negative for HBV, although this was only significant in the linifanib trial. Evaluation of Cochran's Q statistic showed no statistically significant evidence of heterogeneity for any of the main effects (Appendix Table A2, online only).

Median (95% CI) unadjusted OS estimates were 9.44 (8.55 to 10.65), 7.92 (7.36 to 9.23), 8.97 (7.96 to 9.89), and 9.30 (8.58 to 10.52) for patients receiving brivanib, sunitinib, linifanib, and sorafenib, respectively. Hierarchical modeling comparing sorafenib

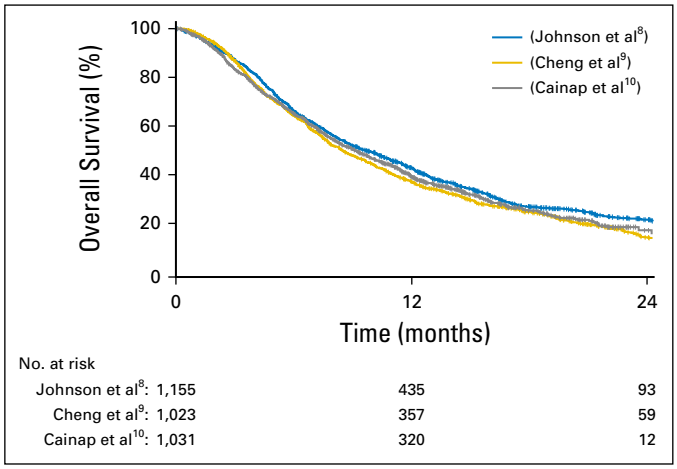


**Fig 1.** Overall survival estimates from the brivanib,[8] sunitinib,[9] and linifanib[10] trials.

  

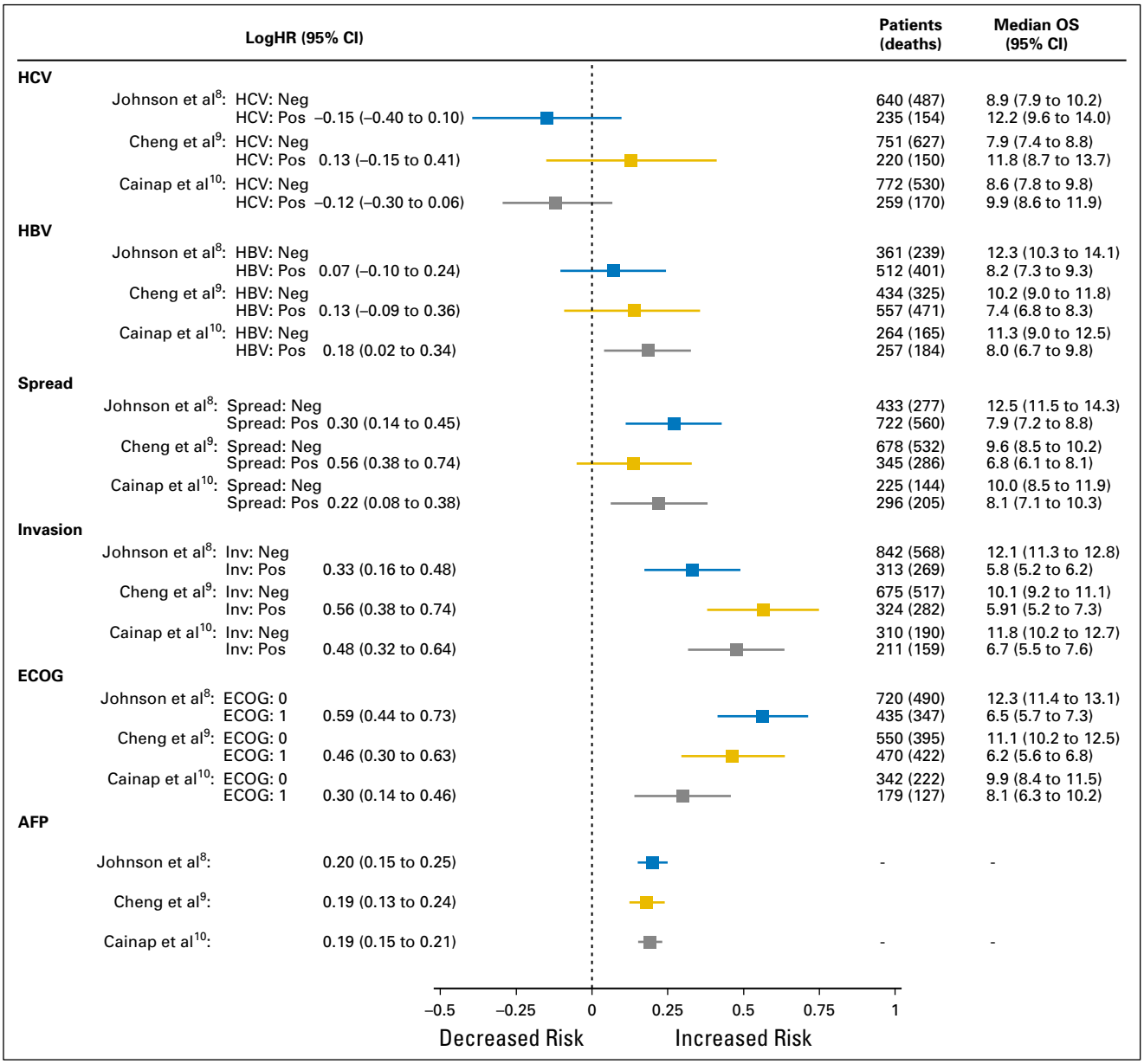


**Fig 2.** Comparison of the effect of prognostic factors on OS from the brivanib, sunitinib, and linifanib trials. AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; Inv, invasion; Neg, negative; OS, overall survival; Pos, positive.

with all alternative therapies did not give sufficient evidence of an overall benefit associated with sorafenib in terms of OS (log HR, −0.13; 95% CI, −0.38 to 0.07).

*Comparisons of sorafenib against other therapies within hepatitis subgroups.* Unadjusted Kaplan-Meier plots showing the OS for sorafenib and other patient groups by their hepatitis status are presented in Figure 3. Comparisons were considered for the four levels created by the combination of HBV and HCV status, namely, (1) HBV negative, HCV negative; (2) HBV positive, HCV negative; (3) HBV negative, HCV positive; and (4) HBV positive, HCV positive. The distribution of patients across these four subgroups is listed in Table 2. Most patients were HBV positive, HCV negative (1,474 of 2,863 patients [51%]). Median (95% CI) OS rates (in months)were 10.42 (9.38 to 11.46), 11.41 (10.19 to 12.63), 7.76 (7.10 to 8.36), and 8.5 (6.22 to 10.78) for the four respective scenarios.

The results of the IPD meta-analyses are given in Figure 4 and show treatment effects comparing sorafenib with other therapies within the four subgroups created by the interaction of HBV and HCV. For patients negative for HBV and HCV (n = 689), there is some evidence of improved survival in patients who received sorafenib, but this was not considered significant because the 95% CI contains zero (log HR, −0.11; 95% CI, −0.28 to 0.09). A similar magnitude of effect was observed for patients who were positive for both HBV and HCV, but with a much larger CI due to reduced patient numbers (n = 72; log HR, −0.11; 95% CI, −0.45 to 0.25). Patients positive for HCV and negative for HBV (n = 628) were the only group to have significant evidence that patients treated with

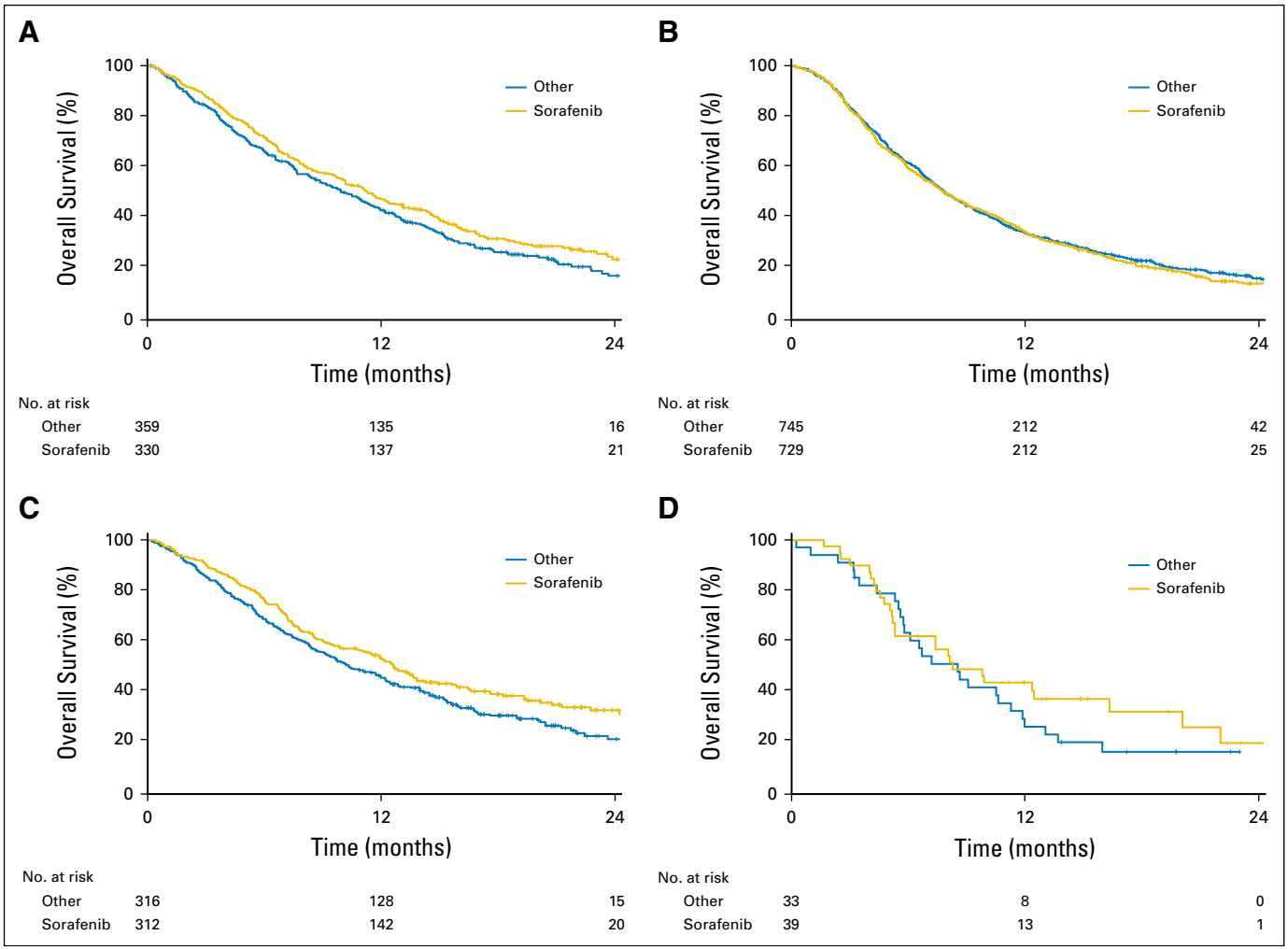


**Fig 3.** Kaplan-Meier plots showing the effect of sorafenib against "other" therapies by hepatitis B virus (HBV) and hepatitis C virus (HCV) status. Overall survival is presented for the following four subgroups: (A) HBV negative, HCV negative; (B) HBV positive, HCV negative; (C) HBV negative, HCV positive; (D) HBV positive, HCV positive.

sorafenib had better OS than the comparator (log HR, −0.26; 95% CI, −0.46 to −0.04). This result is consistent across all sources of data and there is no evidence of heterogeneity based on Cochran's Q statistic (Q = 2.032; $P = .362$). Patients who were HBV positive and HCV negative comprised the largest cohort of data from the three contributing studies (n = 1,474). There was no evidence in this group that there was a beneficial effect on OS attributable to sorafenib; the pooled HR slightly favored the comparator (log HR, 0.05; 95% CI, −0.10 to 0.21). Sensitivity analyses showed little impact on the reported HRs due to methodology applied and did not impact the overall interpretations of the data. Details are listed in Appendix Table A3 (online only). Further investigations were carried out to determine if ethnicity was a confounding factor, but this did not have a significant impact on the model fit in any of the three included studies (Appendix Table A4, online only). The number of grade 3/4 adverse events by type is listed in Table A5 (online only).

**Table 2.** Distribution of Patients Across Hepatitis Status

| | HBV | | |
|---|---|---|---|
| HCV | Neg | Pos | Total |
| Neg | 689 | 1,474 | 2,163 |
| Pos | 628 | 72 | 700 |
| Total | 1,317 | 1,546 | 2,863 |

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; Neg, negative; Pos, positive.

## DISCUSSION

We have carried out an IPD meta-analysis of three phase III RCTs that demonstrates that the effect of sorafenib compared with other treatments for patients with aHCC cannot be considered independent of a patient's HBV and HCV status. For patients who were HBV positive and HCV negative, there was no evidence of any positive effect on OS due to sorafenib, with the HR in this subgroup favoring the comparator, although this was not statistically significant. This patient group comprises 51% of all patients included in the analysis. There was, however, a significant positive effect of sorafenib in the group of patients who were HCV positive and HBV negative

  

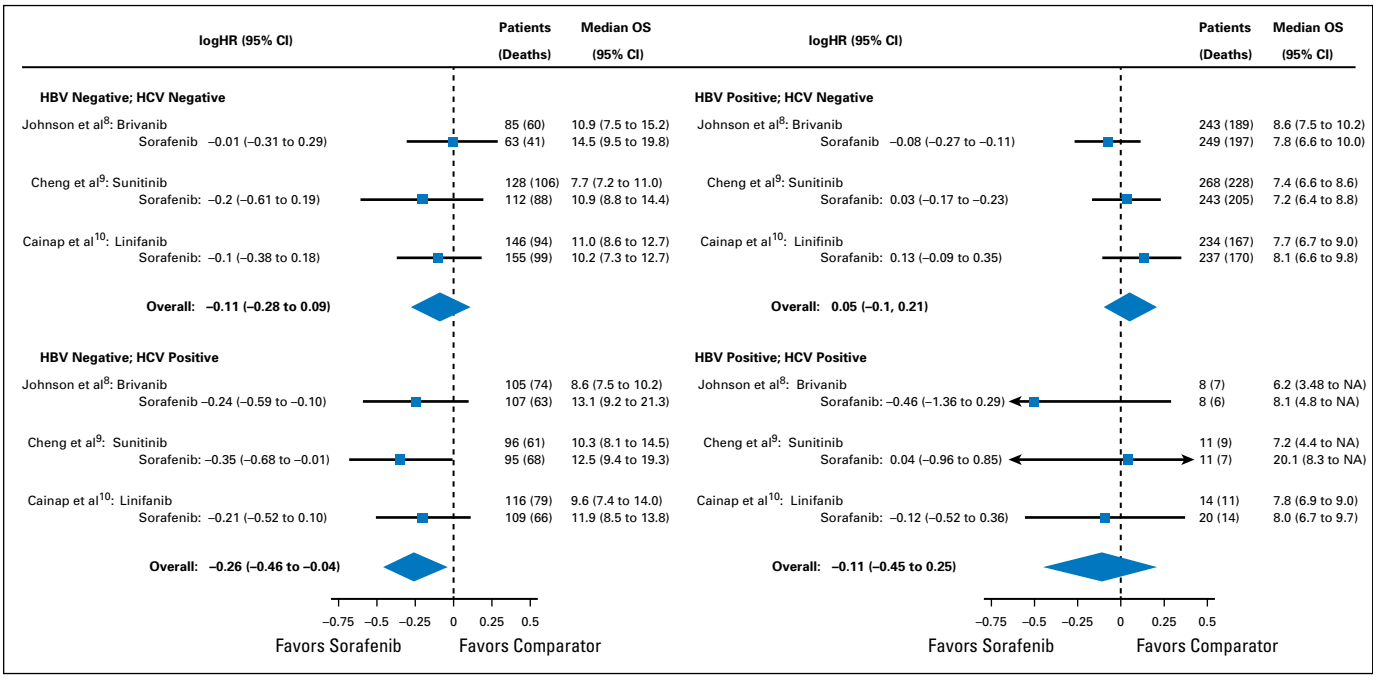


**Fig 4.** Forest plots showing the effect of sorafenib against "other" therapies by the four subgroups created by HBV and HCV subgroups. HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; OS, overall survival.

(n = 628; 22%). For all remaining patients, there was a trend supporting the use of sorafenib, but this was not statistically significant.

Our analysis extends the previous aggregate meta-analysis, which, although lacking the ability of IPD analyses to investigate treatment effects within patient subgroups, did involve additional trials to ours (the SHARP[4] and Asia-Pacific region[5] studies) and concluded that sorafenib might provide more survival benefits to patients positive for HCV. IPD meta-analyses are the gold standard and allow us to analyze trial data that may be more mature than the published results, ensure consistency of analytical techniques across the data sources, and further allow for the inspection of subgroup effects and treatment interactions, which would not be possible using an aggregate meta-analytical approach. Still, the results reported here represent secondary analyses of trial subgroup effects and the evidence provided is not as strong as a RCT, which specifically would look at the effect of sorafenib within each hepatitis subgroup.

The subgroup analysis of the SHARP trial showed that patients positive for HCV had a superior median OS of 14 months compared with 7.4 months in the placebo-treated group, and this benefit was also seen in terms of time to tumor progression (7.6 *v* 2.8 months) and disease control rate (44.2% *v* 29.6%).[6] As noted by Bruix et al,[6] the SHARP trial was not randomized relative to etiology and, therefore, the resulting subgroups were at risk for imbalance. Nonetheless, inspection of the data provided in this subgroup analysis shows that there were a significant number of patients within the HCV-positive subgroup (n = 167; 86 receiving sorafenib and 81 receiving placebo), and that the treated and the placebo groups were, in fact, well balanced with respect to region, age, sex, Child-Pugh class, macrovascular invasion/extrahepatic spread, ECOG PS, and disease stage. These observations, combined with the present detailed IPD meta-analysis and the previous aggregated meta-analysis, support the contention that the impact of sorafenib is largely confined to the patients who are HCV positive. Because the overall benefit of sorafenib in the SHARP study was only 2.8 months compared with placebo, and we found little significant overall effect of sorafenib in the analyses presented here, there is insufficient evidence to support the absolute benefit of sorafenib outside patients positive for HCV. We considered the possibility that ethnicity might be a confounding factor (because HCV and HBV are more prevalent in Western and Eastern populations, respectively), but our analysis did not support this contention. Treatment before trial entry, which may be less intense in Western (and, hence, HCV-positive) populations may also be a confounding factor, but we had insufficient data to exclude this possibility.

There is evidence of genetic diversity[22-25] in HCC that can be linked to specific etiologic factors[22,26] and may permit identification of specific targets for therapy. The reasons for differential response to sorafenib according to etiology remain unclear. Although some in vitro data have suggested that sorafenib inhibits HCV viral replication directly, this has not been borne out in the clinical setting.[7,27] There is evidence of Wnt-pathway dysregulation in about 50% of HCC cases. Of the two major activating classes (CTNNB1 and Wnt-TGFβ), the former appears to be related to HCV infection and activity is modulated by sorafenib in a xenograft model.[13,24,28] HCV has also been shown to upregulate C-RAF,[29] a known sorafenib target, and Braconi et al[30] have shown that HCV proteins can modulate the expression of microRNAs and thereby influence the sensitivity of HCC cells to sorafenib.

Irrespective of the mechanism, our data suggest that in future trials in aHCC, particularly where sorafenib is the control arm, there should be stratification according to etiology. Etiologic differences have already been considered as factors in the interpretation of clinical trials. In the trial of adjuvant sorafenib after surgical resection or local ablation (STORM), although the overall results of the trial were negative, there was a trend for longer time to recurrence in the HCV-related cases.[31]

Following a proposal from the International Committee of Medical Journal Editors[32], it is likely that individual patient data will become accessible to investigators unrelated to the original trial. Thus, as a condition of consideration for publication, it is proposed that authors will be required to include a description of the data-sharing plan in the submitted manuscript. Although the editors considered that "sharing data will increase confidence and trust in the conclusions drawn from clinical trials,"[32(p468)] our study shows how the benefits of access to completed trial data are not necessarily confined to reanalysis of the original hypothesis tested by the trial. Here, by a meta-analysis, we arrive at an answer to a question that was not considered when the trials were conceived and could not have been answered by any of the trials individually. It also illustrates the clinical benefit arising when enlightened pharmaceutical companies are prepared to share their data with an academic unit, even when the primary question does not relate to their products.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

## AUTHOR CONTRIBUTIONS

**Conception and design:** All authors
**Collection and assembly of data:** All authors
**Data analysis and interpretation:** All authors
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Impact of Viral Status on Survival in Patients Receiving Sorafenib for Advanced Hepatocellular Cancer: A Meta-Analysis of Randomized Phase III Trials**

*The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.*

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## Acknowledgment

We thank Bristol-Myers Squibb, Pfizer, and AbbVie for generously giving us access to data from studies in which they acted as sponsor.

## Appendix

### Supplementary Material

Assessment of liver function in clinical trial protocols for targeted treatment of hepatocellular carcinoma (4 papers):

- **Trial A:** Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial[9]
- **Trial B:** Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: Results from the randomized phase III BRISK-FL study[8]
- **Trial C:** Sorafenib in advanced hepatocellular carcinoma[4]
- **Trial D:** Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: Results of a randomized phase III trial[10]

**Table A1.** Trials A to D

| Study Characteristic | Trials* A | B | C | D |
|---|---|---|---|---|
| Liver function: inclusion criteria | | | | |
| Albumin, g/dL | — | ≥ 2.8 | ≥ 2.8 | ≥ 2.8 |
| ALT concentration | ≤ 5 times ULN | ≤ 5 times ULN | ≤ 5 times ULN | ≤ 5 times ULN |
| AST concentration | ≤ 5 times ULN | ≤ 5 times ULN | ≤ 5 times ULN | ≤ 5 times ULN |
| Bilirubin concentration, mg/dL | ≤ 2 (or ≤ 3 with albumin > 3.5 g/dL) | ≤ 3 | ≤ 3 | ≤ 3 |
| Child-Pugh class | A | A | A | A |
| Liver function: exclusion criteria | | | | |
| Ascites | Clinically relevant | Any | — | Moderate |
| Encephalopathy | — | Any | — | > grade 2 per National Cancer Institute |
| Varices | Bleeding within 12 months | Bleeding within 2 months | — | — |
| Bone marrow function: inclusion criteria | | | | |
| Coagulation (INR) | — | ≤ 2.3 (or PT ≤ 6 s longer than control) | ≤ 2.3 (≤ 6 s longer than control) | PT ≤ 6 seconds prolonged |
| Hemoglobin, g/dL | — | ≥ 8.5 | ≥ 8.5 | — |
| Neutrophils (absolute), per μL | ≥ 1,500 | ≥ 1,500 | — | — |
| Platelets | ≥ 75,000/μL | ≥ $60 \times 10^9$/L | ≥ $60 \times 10^9$/L | ≥ $75 \times 10^9$/L or ≥ $50 \times 10^9$/L (if splenomegaly) |
| Other inclusion criteria | | | | |
| Serum creatinine | — | ≤ 2.0 mg/dL | ≤ 1.5 times ULN | ≤ 1.5 times ULN |
| Lipase | — | ≤ 1.5 times ULN | — | — |
| Amylase | — | ≤ 1.5 times ULN | — | — |
| Serum creatinine | — | ≤ 2.0 mg/dL | ≤ 1.5 times ULN | ≤ 1.5 times ULN |
| Previous TACE | Yes | Yes | Yes | Yes, if > 6 months of initiating drug treatment in trial |
| ECOG PS | ≤ 1 | ≤ 1 | ≤ 2 | ≤ 1 |
| Diagnostic confirmation | | | | |
| Cytologic | — | Yes | — | Yes |
| Histologic | Yes | Yes | — | Yes |
| Staging system | | | | |
| BCLC | Yes, retrospectively | Yes, retrospectively | Yes, retrospectively | — |
| CLIP | Yes, retrospectively | — | — | — |
| Stratification | | | | |
| ECOG PS | — | Yes | Yes | Yes |
| Geographical region | Yes | — | Yes | Yes |
| Prior TACE | Yes | — | — | — |
| Site | | Yes | — | — |
| Tumor invasion (extrahepatic+/vascular invasion) | Yes | Yes | Yes | Yes |
| HBV | — | — | — | Yes |
| ECOG PS | — | Yes | Yes | Yes |

Abbreviations: —, unspecified or ambiguous data; BCLC, Barcelona Clinic Liver Cancer (Group); CLIP, Cancer of the Liver Italian Program; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; INR, international normalized ratio; PT, prothrombin time; TACE, transcatheter arterial chemoembolization; ULN, upper limit of normal.

*Overall, in terms of inclusion and exclusion criteria, diagnostic confirmation of hepatocellular carcinoma, and stratification, trials A through D were largely similar.

**Table A2.** Cochran's Q Statistic for the Consistency of Treatment Effects

| Factor | Q | P |
|---|---|---|
| Main Effects | | |
| AFP | 0.27 | .75 |
| ECOG | 5.21 | .058 |
| Invasion | 3.77 | .152 |
| Spread | 1.07 | .58 |
| HBV | 0.88 | .643 |
| HCV | 2.68 | .261 |
| Treatment effects | | |
| HBV: Neg, HCV: Neg | 0.06 | .97 |
| HBV: Neg, HCV: Pos | 0.12 | .94 |
| HBV: Pos, HCV: Neg | 2.03 | .362 |
| HBV: Pos, HCV: Pos | 0.73 | .692 |

Abbreviations: AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; Neg, negative; Pos, positive.

**Table A3.** Results of Sensitivity Analyses on Primary Outcome Measures

| Scenario | Primary Analysis (95% CI) | Two-Stage Meta-Analysis (95% CI) | Unadjusted Meta-Analysis (95% CI) |
|---|---|---|---|
| HBV−; HCV− | −0.11 (−0.28 to 0.09) | −0.09 (−0.27 to 0.09) | −0.15 (−0.34 to 0.04) |
| HBV−; HCV+ | −0.26 (−0.46 to −0.04) | −0.25 (0.45 to −0.07) | −0.25 (−0.51 to −0.05) |
| HBV+; HCV− | 0.05 (−0.10 to 0.21) | 0.01 (−0.10 to 0.13) | 0.06 (−0.08 to 0.22) |
| HBV+; HCV+ | −0.11 (−0.45 to 0.25) | −0.16 (−0.52 to 0.20) | −0.13 (−0.44 to 0.19) |

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

**Table A4.** The Impact of Patient Ethnicity on Etiology as a Predictive Marker

| Study | No. of Patients | European | No. of Patients | Asian |
|---|---|---|---|---|
| Johnson et al[8] (sorafenib *v* brivanib) | | | | |
| HBV−; HCV− | 103 | −0.255 (0.243) | 45 | −0.239 (0.364) |
| HBV−; HCV+ | 80 | −0.761 (0.31) | 114 | −0.2 (0.222) |
| HBV+; HCV− | 36 | 0.053 (0.415) | 450 | 0.067 (0.107) |
| HBV +; HCV+ | 10 | −0.197 (0.534) | 6 | 0.349 (0.418) |
| Cheng et al[9] (sorafenib *v* sunitinib) | | | | |
| HBV−; HCV− | 112 | −0.235 (0.236) | 138 | 0.166 (0.193) |
| HBV−; HCV+ | 64 | −0.521 (0.347) | 131 | −0.257 (0.211) |
| HBV+; HCV− | 21 | −0.03 (0.519) | 503 | −0.111 (0.1) |
| HBV+; HCV+ | 6 | 0.424 (0.79) | 16 | −0.438 (0.308) |
| Cainap et al[10] (sorafenib *v* linifanib) | | | | |
| HBV−; HCV− | 165 | −0.021 (0.076) | 129 | 0.009 (0.221) |
| HBV−; HCV+ | 117 | −0.185 (0.249) | 103 | −0.220 (0.248) |
| HBV+; HCV− | 31 | 0.542 (0.724) | 435 | 0.117 (0.114) |
| HBV+; HCV+ | 4 | N/A | 29 | 0.574 (0.517) |

NOTE. In each study, separate models that include local hepatic spread, ECOG status, local invasion, and log AFP values were included as well as the effect of sorafenib in the four etiologic subgroups created by the interaction of HBV and HCV. Appendix Table A5 lists the number of patients in each subgroup as well as the log hazard ratios in the four etiologic subgroups of interest. In none of the studies did the inclusion of ethnicity, either with or instead of etiologic status, improve the model fit in terms of the observed AIC. The results show there are obvious differences in the etiologic status of European and Asian populations, with patients negative for both HBV and HCV being more prevalent in European populations and patients positive for HBV and negative for HCV being more prevalent in Asian populations. Comparing the effect of sorafenib with alternative therapies, the effects were reasonably consistent across the three trials. For the main subgroup of interest (ie, HBV negative; HCV positive), there is some evidence in the brivanib and sunitinib trials that there were increased effects due to sorafenib in the European populations (log HR, −0.761 and −0.521 observed, respectively); however, these occurred in relatively small subgroups and were not repeated in the linifanib study.

Abbreviations: AFP, alpha-fetoprotein; AIC, Akaike information criterion; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; N/A, not applicable.

**Table A5.** Summary of Toxicity by Trial

| | Cheng et al[9] | | | | Johnson et al[8] | | | | Cainap et al[10] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sunitinib (n = 526) | | Sorafenib (n = 542) | | Brivanib (n = 575) | | Sorafenib (n = 575) | | Linifanib (n = 510) | | Sorafenib (n = 519) | |
| Adverse Event | N | % | N | % | N | % | N | % | N | % | N | % |
| Overall | 432 | 82.1 | 402 | 74.2 | 387 | 67.3 | 375 | 65.2 | 435 | 85.3 | 389 | 75 |
| Thrombocytopenia | 156 | 29.7 | 25 | 4.6 | — | — | — | — | 27 | 5.3 | 11 | 2.1 |
| Diarrhea | 38 | 7.2 | 49 | 9 | 36 | 6.3 | 40 | 7 | 61 | 12 | 48 | 9.2 |
| Decreased appetite | 30 | 5.7 | 20 | 3.7 | 48 | 8.3 | 17 | 3 | 22 | 4.3 | 13 | 2.5 |
| Hand-foot syndrome | 70 | 13.3 | 114 | 21.1 | 12 | 2 | 86 | 15 | 70 | 13.7 | 77 | 14.8 |
| Neutropenia | 135 | 25.7 | 12 | 2.2 | — | — | — | — | 20 | 3.9 | 12 | 2.3 |
| Anemia | 49 | 9.3 | 22 | 4 | — | — | — | — | 15 | 2.9 | 28 | 5.4 |
| Fatigue | 33 | 6.3 | 21 | 3.9 | 84 | 14.5 | 38 | 7 | 49 | 9.6 | 25 | 4.8 |
| Leukopenia | 69 | 13.2 | 5 | 0.2 | — | — | — | — | 18 | 3.5 | 12 | 2.3 |
| Nausea | 6 | 1.1 | 5 | 0.9 | 12 | 2 | 2 | 0.3 | — | — | — | — |
| Abdominal pain | 20 | 3.8 | 14 | 2.6 | 40 | 7 | 31 | 5.3 | — | — | — | — |
| Pyrexia | 3 | 0.6 | 3 | 0.6 | 3 | 0.5 | 2 | 0.3 | — | — | — | — |
| Hypertension | 20 | 3.8 | 15 | 2.8 | 77 | 13.3 | 31 | 5.3 | 106 | 20.8 | 45 | 10.6 |
| Rash | 4 | 0.8 | 18 | 3.3 | 6 | 1 | 12 | 2 | — | — | — | — |
| Vomiting | 14 | 2.7 | 7 | 1.3 | 17 | 3 | 3 | 0.5 | 22 | 4.3 | 4 | 0.8 |
| Abdominal distention | 12 | 2.3 | 7 | 1.3 | | | | | 23 | 4.5 | 14 | 2.7 |
| Constipation | 2 | 0.4 | 1 | 0.2 | 2 | 0.3 | 1 | 0.2 | — | — | — | — |
| Stomatitis | 8 | 1.5 | 2 | 0.4 | — | — | — | — | — | — | — | — |
| Ascites | 27 | 5.2 | 18 | 3.3 | — | — | — | — | 31 | 6.1 | 17 | 3.3 |
| AST level increased | 46 | 8.8 | 49 | 9 | 87 | 15 | 98 | 17 | 62 | 12.2 | 65 | 12.5 |
| Asthenia | 34 | 6.5 | 24 | 4.4 | | | | | 36 | 7.1 | 11 | 2.1 |
| Weight decreased | 5 | 1 | 8 | 1.5 | 23 | 4 | 12 | 2 | — | — | — | — |
| Alopecia | 0 | 0 | 1 | 0.2 | | | | | — | — | — | — |
| Hyponatremia | — | — | — | — | 133 | 23 | 53 | 9.2 | 19 | 3.7 | 17 | 3.3 |
| ALT level increased | — | — | — | — | 42 | 7.3 | 46 | 8 | 11 | 2.2 | 25 | 4.8 |
| Headache | — | — | — | — | 6 | 1 | 2 | 0.3 | | | | |
| Hyperbilirubinemia | — | — | — | — | 69 | 12 | 52 | 9 | 32 | 6.3 | 21 | 4 |
| Dizziness | — | — | — | — | 6 | 1 | 2 | 0.3 | — | — | — | — |
| Hepatic encephalopathy | — | — | — | — | — | — | — | — | 37 | 7.3 | 17 | 3.3 |
| Hypokalemia | — | — | — | — | — | — | — | — | 24 | 4.7 | 12 | 2.3 |
| Platelet count decreased | — | — | — | — | — | — | — | — | 17 | 3.3 | 10 | 1.9 |
| Hypoglycemia | — | — | — | — | — | — | — | — | 16 | 3.1 | 4 | 0.8 |
| Blood bilirubin level increased | — | — | — | — | — | — | — | — | 23 | 4.5 | 18 | 3.5 |

Abbreviation: —, no data.