Survival and Cost-Effectiveness of Sorafenib Therapy in Advanced Hepatocellular Carcinoma: An Analysis of the SEER-Medicare Database

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Abbreviations:
HCC – hepatocellular carcinoma
ICER – incremental cost-effectiveness ratio
ECOG – Eastern Cooperative Oncology Group
AASLD - American Association for the Study of Liver Disease
EASL - European Association for the Study of the Liver
BCLC – Barcelona Clinic Liver Cancer
GIDEON - Global Investigation of Therapeutic Decision In Hepatocellular Carcinoma and if its Treatment with Sorafenib
HCV – hepatitis C virus
SEER- Surveillance Epidemiology and End Results
AJCC - American Joint Committee on Cancer
NCI – National Cancer Institute
EGD – esophagogastroduodenoscopy
SD - standard deviation
IQR – interquartile range
HR – hazard ratio
BOOST - B Child Patient–Optimization Of Sorafenib Treatment

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ABSTRACT

Sorafenib is the only chemotherapeutic approved for treatment of advanced hepatocellular carcinoma (HCC.) However, its effectiveness in patients with Child Pugh B cirrhosis and any moderating effects of health system characteristics are unclear. We aimed to examine the survival and cost-effectiveness associated with sorafenib in elderly patients with advanced HCC. We performed an analysis of Medicare beneficiaries with HCC diagnoses from 2007-2009. We compared advanced stage patients with HCC (AJCC stage III/IV) who received sorafenib within 6 months of diagnosis (and were otherwise untreated) to advanced stage patients with HCC who received no therapy (control.) We performed univariate and multivariate analyses to identify predictors of survival. Incremental cost effectiveness ratios (ICERs) were calculated for sorafenib-treated and control patients. We included 228 sorafenib-treated patients and 870 control patients. The median survival of the sorafenib-treated patients was 150.5 days versus 62 days for control patients. In multivariate analysis, significant predictors of improved survival were treatment with sorafenib (HR: 0.66; 95% CI: 0.57-0.77), being seen at a National Cancer Institute-designated cancer center (HR: 0.77; 95%CI: 0.62-0.97) or transplant center (HR: 0.77; 95% CI: 0.65-0.93.) Predictors of worse survival included Stage IV disease (HR: 1.40; 95%CI: 1.24-1.58), decompensated cirrhosis (HR: HR: 1.49; 95%CI: 1.30-1.70,) and treatment in an urban setting (HR: 1.45; 95% CI: 1.21-1.73.) Although sorafenib use was associated with a survival benefit (0.61, 95% CI: 0.47-0.79) among patients with decompensated cirrhosis, the median survival benefit was 31 days and it was not cost-effective with an ICER of $224,914 per life year gained. Conclusions: Sorafenib is associated with improved survival in elderly patients with advanced HCC; however it is not cost-effective among those with hepatic decompensation.

Hepatocellular carcinoma (HCC) is an increasingly incident and morbid malignancy.(1) Patient tumor burden, functional status, and underlying liver function are recognized predictors of patient mortality with HCC.(2) Unfortunately, many patients present with advanced HCC and can only be treated with palliative therapies, which are designed to extend life but are not capable of achieving cure. Sorafenib, a multikinase inhibitor, is the only approved systemic therapy for patients with unresectable or metastatic disease.(3) In the SHARP trial, a randomized control trial among Child-Pugh class A patients with a Eastern Cooperative Oncology Group (ECOG) status of 0-1 and advanced HCC, sorafenib increased survival by approximately 3 months compared to placebo.(4) The American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL) guidelines recommend sorafenib as the first-line therapy for Barcelona Clinic Liver Cancer (BCLC) stage C patients, i.e. those with unresectable HCC, ECOG status of 1-2, and Child-Pugh class A or B liver function.

However, the benefit of sorafenib in patients with advanced liver disease (i.e. Child-Pugh class B), particularly those with ascites or hepatic encephalopathy, is unclear given limited available data.(3) The Global Investigation of Therapeutic Decision In Hepatocellular Carcinoma and if its Treatment with Sorafenib (GIDEON) data suggest sorafenib is well tolerated by patients with Childs-Pugh class B cirrhosis and advanced HCC with a median survival of 5.2 months, but this post-marketing study did not have a comparator arm so analyses of survival benefit have relied on comparisons to historical controls.(5, 6) Further, we lack an understanding of how health system characteristics, e.g. being seen at a tertiary care referral center, impact treatment effectiveness and survival. The population of patients with HCC is shifting to a more elderly demographic, largely due to an aging population with chronic hepatitis C virus (HCV) infection; thus, the impact of age and accumulated comorbidities is becoming increasingly relevant when making HCC treatment decisions.(7)

To address the gaps in the existing literature, we aimed to analyze the Surveillance Epidemiology and End Results (SEER) Medicare linked database to determine the survival benefit and cost-effectiveness associated with sorafenib treatment for advanced HCC in clinical practice.

METHODS

We performed a secondary analysis of the SEER-Medicare data linked dataset with Part D data for new diagnoses of HCC from 2007-2009. The details of SEER-Medicare data are described elsewhere.(8) Part D is a United States federal program instituted in 2006 that subsidized medications for Medicare beneficiaries. The Part D data included in SEER-Medicare includes medications prescribed, number of prescriptions filled, and medication costs.(9)

Patient Selection

We included Medicare patients with continuous enrollment in Medicare Parts A & B from 12 months prior to diagnosis through the end of follow-up (December 31, 2010), allowing up to a 3-month gap in coverage per year. We included SEER-Medicare patients with a diagnosis of HCC (International Classification of Diseases for Oncology, Third Edition, histology codes 8170 through 8175 and 8180 for HCC and site code C22.0 for liver.)(10) Patients with another malignant primary tumor diagnosed prior to HCC diagnosis and patients who had HCC diagnosed upon death were excluded. We included American Joint Committee on Cancer (AJCC) Stage III and IV HCC based on the SEER staging guide to identify patients with advanced HCC. Patients with missing data on tumor stage were excluded. Those with dates of birth that differed between Medicare and SEER by more than a year were removed from the analysis, as were any patients with autopsy or death certificate-only records. We compared patients who received only sorafenib therapy through the Part D program to patients who received no therapy (control group) during the study period. To identify control patients, we

excluded patients who had any ICD-9 codes for surgical resection, liver transplantation, liver directed therapies (ablative procedures, radiation therapy, transarterial chemoembolization, transarterial radioembolization,) and other systemic therapies. Patients were followed from HCC diagnosis to death or end of follow-up.

Covariates

Covariates of interest included patient-level factors (age, gender, race, comorbidities, and presence of hepatic decompensation,) and system-level factors, (region of country, residence in an urban vs. rural area [as defined by residence in a metropolitan statistical area,] association with liver transplant center, and National Cancer Institute (NCI)-designation.) We calculated Charlson comorbidity index using data from 12 months prior to HCC diagnosis, excluding codes for liver disease, as previously described.(11) We excluded liver disease codes from the comorbidity index as nearly all patients had underlying chronic liver disease, if not cirrhosis (12); further, we were interested in exploring the prognostic significance of hepatic decompensation independent of other comorbidities. We developed a composite variable for liver decompensation that included administrative codes for: 1) ascites (ICD-9 789.5x) and procedural coding for paracentesis (HCPCS 49080 - 49084); 2) hepatic encephalopathy (ICD-9 572.2, 070.4x, 070.6x) and medication codes from Part D for neomycin, lactulose and rifaximin; or 3) esophageal varices (ICD-9 456.0, 456.1, 456.2) and procedural coding for esophagogastroduodenoscopy (EGD) with variceal banding (HCPCS 43205, 43244, 43251, 43999, 46934). We performed a sensitivity analysis excluding esophageal varices from the definition of decompensation, as its inclusion without overt variceal bleeding is controversial.

ECOG Sensitivity Analysis

ECOG score is an important prognostic marker in patients with advanced HCC, both for staging and prognosis, however it is not captured in the SEER-Medicare dataset. Therefore we

performed a sensitivity analysis to account for potential unmeasured confounding from ECOG.(13) Based on previously published data, our sensitivity analysis examined the hazard ratios associated with ECOG 3-4 status of 1.5 and 2.0 and its impact on sorafenib associated survival benefit in the multivariate model.(14) We varied the proportion with high ECOG status in the treatment group from 0-50% in increments of 10% and from 0-100% in increments of 10% in the control group.

Cost Analysis

Total costs from the Medicare perspective were compiled using Medicare Part A, B, and D data files from diagnosis to the end of follow-up. We compared costs for sorafenib-treated patient and control patients and calculated incremental cost-effectiveness ratios (ICERs) per life year gained. ICER is defined as the difference in costs divided by year of life gained, and compared to the accepted threshold of $100,000 per life-year for cost-effective treatments.(15-18) We used life-year gained instead of quality life-year gained, as there are no available validated quality of life utility adjustments for patients on sorafenib therapy. All costs were inflated to 2015 US dollars. We performed a stratified analysis based upon the presence of liver decompensation, as defined above.

To examine the cost effectiveness ratio, we used a sensitivity analysis where our empirical distribution was resampled using replacement, giving us a total of 500 bootstrap permutations of the data. We modeled the ICER statistic value for each of the 500 sets of data and checked its cumulative density function, producing a cost-effectiveness acceptability curve.(19, 20) To assess the variation of the sample we considered the 2.5% and 97.5% nonparametric percentiles along with the median value. We also conducted traditional one-way sensitivity analyses by varying survival of the sorafenib treated group by 10% and 40% to test the robustness of our ICER estimates.

Statistical Analysis

Patient characteristics were compared between treated and control patients. Fisher exact and Kuskal Wallis tests were used for categorical and continuous variables, respectively, except age, which was symmetrically distributed and was evaluated with Student's t test. The variables with distributions that deviated from normality were reported by median and interquartile range (Q1, Q3) and those with normal distribution were reported as mean ± standard deviation (SD).

We conducted Kaplan-Meier survival analysis with log rank tests to compare survival from the time of HCC diagnosis between strata. Propensity score adjustment was used to balance the cohorts using 1:1 nearest neighbor matching, accounting for the differences between the sorafenib-treated and untreated cohorts in our univariate analysis. The propensity score algorithm selected the other predictor variables by predicting the treatment variable in a logistic regression. From that a predicted outcome comprised of a combination of the predictor variables with the slopes creates a propensity score, and this was used to match the treatment group subjects to the best control group subjects and discard the remainder. We also performed propensity score matching for the subset of patients with decompensated cirrhosis. We constructed a multivariate Cox model to identify predictors of survival. The primary independent variable of interest was sorafenib treatment, with other covariates described above. We used variance inflation factors to test for collinearity in the model variables with the intention of sequentially removing variables where significant collinearity was present. However no collinearity was found in any of our multivariate analyses, as all VIF values were less than 2.5. We also tested for any interaction between relevant variables (i.e. sorafenib treatment and decompensation) to determine if a stratified analysis was warranted, however no significant interactions were seen. We performed a sensitivity analysis to account for immortal time bias by conducting a time-dependent covariate survival analysis for sorafenib use. All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC) and R version 3.2.2. The R package "MatchIt"

was used for the propensity scores, the package “survival” was used for Cox Proportional Hazards regression, the package “RItools” was used for evaluation of propensity scores balance and “rms” was used to create the Kaplan Meier survival curves.(21-27)

RESULTS

From 2007-2009, 8,102 patients with a new diagnosis of HCC were identified in the SEER-Medicare data set. A total of 5,125 patients had AJCC stage III or IV disease and of these 1,098 met the inclusion criteria for the study.(Supplemental Figure 1)

Baseline Characteristics

A total of 228 patients were included in the sorafenib treated group and 870 patients were included in the untreated group. The characteristics of the two groups are shown in Table 1. Patients in the untreated group were significantly older and more likely to be White or Black than sorafenib-treated patients. There were no significant differences in gender distribution or representation in regional areas of the United States. The two groups had similar AJCC cancer stage at diagnosis and prevalence of decompensated cirrhosis, although the untreated group had a greater proportion of patients with a Charlson comorbidity index greater than 3. There were no differences between the groups regarding being seen at a NCI-designated cancer center or transplant center, but patients in the untreated group were significantly less likely to be seen at a teaching hospital.

Survival

Median survival of the entire cohort was 90 (IQR: 31-184) days, with 3-month, 6-month, and 1-year survival rates of 49.0%, 28.0%, and 12.0%, respectively. For sorafenib treated patients, mean time from HCC diagnosis to sorafenib initiation was 32.6 (±40.4) days.

Sorafenib-treatment was associated with a significantly better overall survival than untreated patients (p<0.001, Figure 1a). Median survival for patients treated with sorafenib from time of HCC diagnosis was 150.5 (IQR=62-273) days, while the median survival of the control groups was 62 (IQR=31-153) days. The 3-month, 6-month, and 1-year actuarial survivals for the sorafenib group and untreated group were 67.5%, 41.7%, and 18.0% vs. 44.1%, 24.4%, and 10.5%, respectively.

Multivariate analysis of the entire cohort showed there was a lower risk of mortality for sorafenib-treated patients (HR 0.66, 95%CI 0.57-0.77,) patients seen at a NCI-designated center (HR 0.77, 95%CI 0.62-0.97,) or at a transplant center (HR 0.77, 95%CI 0.62-0.97.) Independent predictors of higher mortality included stage IV tumor burden (vs. stage III) (HR 1.40, 95%CI 1.24-1.58,) urban setting (HR 1.45, 95%CI 1.21-1.73,) and presence of hepatic decompensation (HR 1.49, 95%CI 1.30-1.70.) (Table 2) In a sensitivity analysis, removal of esophageal varices from the decompensation variable resulted in a similar hazard ratio in the multivariate model (HR: 1.43, 95% CI 1.29-1.59.) In another sensitivity analysis to account for immortal time bias, we considered sorafenib use as a time dependent variable, and we found that its use was associated with improved survival, however this failed to reach statistical significance (HR: 0.87, 95% CI: 0.74-1.01.)

Stratification by Decompensation

Sorafenib-treatment in patients with compensated liver disease (i.e. absence of ascites, hepatic encephalopathy or esophageal varices) was associated with a significantly better survival than untreated patients with compensated liver disease (p=0.002). The median survival of sorafenib-treated patients was 153 days (IQR=90-275.8) vs. 90.5 days (IQR=31-212) for untreated patients. Actuarial 3-month, 6-month and 1-year survival rates were 71.8%, 45.8%, and 19.7% vs. 50.0%, 28.8%, and 13.6%, respectively.

Sorafenib-treatment in patients with evidence of hepatic decompensation also was associated with a significantly better survival than untreated patients with decompensated liver disease ($p < 0.001$, Figure 1b). Although the relative benefit associated with sorafenib was similar to those with compensated liver disease, the absolute benefit associated with sorafenib in patients with hepatic decompensation was smaller. Median survival of the sorafenib-treated patients with hepatic decompensation was 92 days (IQR=61-205) vs. 61 days (IQR=31-122) for untreated patients. Actuarial 3-month, 6-month, and 1-year survival rates in sorafenib-treated and untreated patients were 60.5%, 34.9%, and 15.1% vs. 35.7%, 18.0%, and 5.9%, respectively. For patients with only one decompensation coded (n=59 for treatment and n=222 for control,) the 3-month, 6-month, and 1-year survival rates were 57.6%, 39.0%, and 20.3% vs. 36.9%, 18.9%, and 6.3%, respectively ($p<0.001$.)

Table 3 shows the multivariate analysis of factors associated with survival in patients with hepatic decompensation (n=422). Treatment with sorafenib (HR: 0.61, 95% CI: 0.47-0.79) and being seen at an NCI designated center (HR: 0.62, 95% CI: 0.45-0.86) were both associated with improved survival, while stage IV (vs stage III) disease (HR: 1.27, 95% CI 1.04-1.56) and treatment in an urban setting (HR: 1.57, 95% CI: 1.14-2.16) were associated with increased mortality.

Propensity Score Adjusted Analysis

After matching sorafenib-treated to untreated patients with propensity scores, we balanced all available covariates individually and globally, removing baseline differences between the groups (Hansen-Bowers Chi-square 4.0, p=1.000.) After discarding the unmatched population, there were 228 sorafenib-treated patients and 228 untreated patients remaining. Patient survival is shown in Figure 1c, with significantly better survival among sorafenib-treated patients than untreated patients ($p<0.001$). Median survival was 150.5 (IQR=62-273) days in the sorafenib-treated group and 62 (IQR=31-213) days in the control

group. The 3-month, 6-month, and 1-year actuarial survival for the sorafenib treated group and untreated group were 67.5%, 41.7%, and 18.0% vs. 49.6%, 28.5%, and 11.0%, respectively. In multivariate propensity score-adjusted analysis, sorafenib treated patients had a significantly lower risk of mortality (HR 0.55, 95%CI 0.46-0.67.) Factors significantly associated with higher risk of mortality in multivariate analysis included stage IV tumor burden (vs stage III) at diagnosis (HR 1.33, 95%CI 1.10-1.61), presence of hepatic decompensation (HR: 1.74, 95%CI 1.40-2.16) and being treated at an urban center (HR 1.94, 95%CI 1.40-2.68); (Table 2.)

We also performed propensity score matching of only the decompensated patients and included 81 patients in the sorafenib treated group and 81 patients in the untreated group. Patient survival was again better in the sorafenib treated patients (p=0.004.) The median survival was 92 (IQR=61-185) days in the sorafenib-treated group and 61 (IQR=31-122) days in the control group. The 3-month, 6-month, and 1-year actuarial survival for the sorafenib treated group and untreated group were 58.0%, 34.6%, and 16.1% vs 34.6%, 18.5%, and 4.9%, respectively. In the multivariate propensity score-adjusted analysis, sorafenib treated patients had a significantly lower risk of mortality (HR: 0.62, 95% CI: 0.45-0.87) as did patients who were seen at a transplant center (HR: 0.59, 95% CI: 0.38-0.92); (Supplemental Table 1.) Stage IV (vs Stage III) disease was the only factor associated with worse survival (HR: 1.48, 95% CI: 1.05-2.08.)

Predictors of Survival Among Sorafenib-Treated Patients

Predictors of survival among sorafenib-treated patients on univariate analysis were treatment in an urban setting (HR 1.61, 95% CI 1.20-2.17 p=0.002), age (HR 0.98, 95% CI 0.97-1.00, p=0.028), and presence of hepatic decompensation (HR 1.40, 95% CI 1.06-1.84, p=0.019.) Median survival of sorafenib-treated patients with and without hepatic decompensation was 92 and 153 days, respectively (Figure 2a; p=0.02). Similarly, overall survival among sorafenib-treated patients was significantly associated with the number of

unique hepatic decompensation codes for each patient (p=0.008, Figure 2b). Independent predictors of survival among sorafenib-treated patients in a multivariate analysis are shown in Supplemental Table 2. Being treated in an urban setting was the only significant predictor of mortality (HR: 2.12; 95% CI: 1.32-3.41). Hepatic decompensation was associated with increased risk of mortality (HR: 1.29 95% CI 0.94-1.76), but this difference did not reach statistical significance on multivariate analysis.

ECOG Sensitivity Analysis

The results of the ECOG score sensitivity analysis are shown in Table 4. In the case where the ECOG 3-4 score associated HR was assumed to be 1.5, sorafenib was no longer associated with improved survival when the prevalence of ECOG 3-4 was greater than 40% for the control group and 0% for the sorafenib-treated patients. If there are any sorafenib-treated patients in the ECOG 3-4 group, the survival benefit associated with persists with even higher rates of ECOG 3-4 status in the control group.

In the case of an assumed HR of 2.0 associated with ECOG 3-4 status, sorafenib is associated with a survival benefit when the prevalence of ECOG 3-4 is lower than 20% in the control group. This threshold again increases with increasing prevalence of ECOG 3-4 in the sorafenib treated group. Once the prevalence of ECOG 3-4 becomes very high in the control group (>60%,) however, sorafenib is associated with worse survival when compared to controls. (Supplemental Table 3.)

Costs

We analyzed cost differences between sorafenib-treated and untreated groups, as shown in Table 5. Based on accepted thresholds, sorafenib therapy appears to be cost-effective in both the overall cohort (ICER: $84,250) and propensity-matched cohorts (ICER: $81,249.) However, sorafenib is no longer cost-effective when analysis is limited to patients with

decompensation, with an ICER of $224,914 per life year gained in the overall decompensated cohort and $188,065 per life year gained in the propensity-matched decompensated cohort.

In a one-way sensitivity analysis of the overall cohort, we found varying the median survival seen with sorafenib 10% resulted in an ICER range of $72,005-$101,513 and 40% resulted in an ICER range from $50,142-$263,469.

We created two different ICER bootstrap samples—one for the overall comparison and one for the propensity score sample. The median values of the distributions were higher than our observed statistic so the percent of times for which the ratio was less than the standard cutoff ($100,000) might be biased upwards. The median ICER for the overall set was $96,327 (95% CI: $70,253 -$193,573) and $110,982 (95% CI: $67,701-$321,127) for the propensity score set. Given these ranges we cannot conclude that our realized estimates were significantly less than $100,000. We found that 55% of the ICER statistics were below $100,000 for the overall sample (Figure 3a) and 41% for the propensity score set (Figure 3b.)

DISCUSSION

Although sorafenib has been demonstrated to be efficacious in patients with advanced HCC, compensated liver disease, and good performance status, effectiveness data from real world clinical settings, particularly those with liver decompensation, are limited. Our study shows sorafenib is associated with a similar survival benefit (88 days) among elderly patients with advanced HCC as that seen in the SHARP trial. However, absolute median survival for both the treatment and control groups were shorter than observed in the SHARP trial, likely due to advanced patient age and higher rates of comorbid conditions, including hepatic decompensation.(4) Among the subgroup of patients with hepatic decompensation, the benefit of sorafenib was modest (31 days) and treatment is no longer cost-effective. Notably the time dependent sensitivity analysis showed that sorafenib was associated with an improved survival, however this did not reach statistical significance. This analysis accounts for immortal time bias,

which is especially salient in this population, given high early mortality after diagnosis of advanced HCC. We did not adjust the cost analysis for immortal time bias, but sorafenib may not be cost effective when taking this factor into account.

An interim analysis of GIDEON, demonstrated sorafenib is often used in patients with liver dysfunction, as nearly 40% had Child Pugh class B or C disease at time of sorafenib initiation.(28) As expected, sorafenib was well tolerated and time-to-progression was similar (4.7 vs 4.4 months, respectively); however, median survival was longer in Child-Pugh class A (13.6 months [95% CI: 12.8-14.7]) than Child-Pugh class B patients (5.2 months [95% CI: 4.6-6.3].) (29) Notably, interpretation of GIDEON data is limited by the lack of a comparator group with untreated patients to assess any survival benefit. Prior studies have highlighted the importance of effectiveness data, as several efficacious treatments fail to show a similar benefit when used in clinical practice given differences in providers, treatment management, and patients.(30)

Although there is an ongoing randomized control trial to test the efficacy and safety profile of sorafenib in Child-Pugh class B patients--the B Child Patient–Optimization Of Sorafenib Treatment (BOOST) study(31), which may better define the role for sorafenib in the decompensated population, these data will not be available for years. In the interim, sorafenib use among patients with hepatic decompensation continues to be common, accounting for over one-third of patients in GIDEON. Our data may serve as a guide while awaiting further data from BOOST.

The cost-effectiveness of sorafenib was not previously well defined, as many prior cost-effectiveness analyses restricted costs to medications alone, without accounting for comprehensive costs of the treatment strategy.(32, 33) Although non-medication costs are a large contributor to overall costs for many other cancers, we were surprised to find medication costs through Part D were the largest contributor to the difference in costs between sorafenib-treated and control groups. This difference in relative contributions from medication costs might be related to patients' short life expectancy and limited time for other health care usage. While

costs alone should not be used to make medical decisions, the ICERs in our analysis are contextualized with potential survival benefits.(18) Although sorafenib appears cost effective among all comers based on our base case analysis, it is of modest survival benefit and not cost effective in those with hepatic decompensation. Therefore, our data suggest providers may consider best supportive care and earlier referral to palliative care for elderly patients with hepatic decompensation and advanced HCC.

On sensitivity analysis, the ICER only varied significantly above the $100,000 threshold with large changes in survival benefit associated with sorafenib, but was otherwise insensitive to smaller changes in sorafenib associated survival benefit. The bootstrapped data show some uncertainty around the ICER estimation--a high proportion of the estimations in both the base-case and propensity-score matched analysis fall outside the cost-effective range, which further calls into question the cost-effectiveness of sorafenib therapy.

Patients treated at transplant centers and/or NCI-designated centers had better outcomes. These associations may be driven by several factors such as higher rates of multidisciplinary care or better management of liver complications, which have been shown to improve survival(34); alternatively, this association may simply represent a referral or selection bias, with healthier patients who have a better prognosis being more likely to seek care at a tertiary care center. Further studies are needed to explore these associations; if confirmed and related to a difference in care delivery, this may suggest that treatment of advanced HCC patients be focused in expert, high-volume centers. Interestingly, being treated in an urban setting was consistently associated with worse survival in our study. While urban residents may have better access to NCI-designated or transplant centers for treatment, there is evidence that rural patients may have a more consistent source of healthcare and less likely to delay care.(35) There was no collinearity between urban setting and being seen at a transplant or NCI-designated center, which suggests urban patients were not more likely to be seen at these centers.

Our study has many strengths and weaknesses that warrant attention. Our data are limited by the use of administrative Medicare coding, which can be subject to omission or misclassification. Our hepatic decompensation variable relied on ICD-9 coding, so not all patients with decompensation in both groups were likely captured. Second, SEER-Medicare data has limited data for HCC tumor stage; the AJCC staging system is not widely endorsed for HCC due to lack of important prognostic information including Child-Pugh classification and performance status. It is possible that some patients in our analysis had Child-Pugh class C or ECOG status 3-4, resulting in BCLC stage D disease for whom sorafenib is not recommended. Our ECOG sensitivity analysis showed that relatively high proportions of patients in the control group would have to have ECOG 3-4 status to significantly impact the results of the study, even in scenarios with high associated hazard ratios for ECOG 3-4 status. Third, prescriptions and refills in Part D data are proxies for actual sorafenib use—thus we are limited in knowing if patients actually were taking the prescribed medications. Similarly, control patients could have been taking sorafenib outside the Part D program, however we attempted to account for this by only including patients with continuous enrollment in the Medicare program. Fourth, it is possible the control group had characteristics that made them poor treatment candidates with worse survival; however, we attempted to account for this potential selection bias in our propensity score analysis for both the overall sample and the decompensated patients. An important consideration is that the control group was completely untreated and thus may have characteristics that bias them toward worse survival, so the lack of a greater survival benefit for the sorafenib treated group in this study is striking. Fifth, we lacked data on quality of life, which limited our ability to quality adjust our results for the cost-effectiveness analysis. Sorafenib has numerous side effects which may impact patient quality of life and should be considered when considering effectiveness of treatment. Finally, these data are in elderly Medicare beneficiaries, so the data may not be applicable to younger patients with HCC. Nonetheless this study

examines the real world benefit of sorafenib therapy, quantifying the impact of decompensation on outcomes and the cost-effectiveness of treatment.

In conclusion we have shown that sorafenib is associated with a survival benefit and is cost-effective in elderly patients with advanced HCC. However, survival benefit is diminished when hepatic decompensation is present, likely due to competing risk of death from underlying liver disease. The results are particularly salient as HCC is projected to increase in elderly age groups in the coming decades.(36) In addition, the results of this study are clinically relevant as a high proportion of patients with advanced HCC present with hepatic decompensation or become decompensated during the course of therapy.(29) Decompensated patients with advanced HCC are often treated with sorafenib in real world settings, however our data show that this is not a cost-effective treatment in this population due to the high costs of sorafenib and the marginal survival benefit associated with treatment.(29) While awaiting more granular, prospective data on sorafenib effectiveness in patients with decompensated liver disease, careful selection of patients is warranted when considering treatment of patients with advanced HCC with sorafenib.

Figure Legend

Figure 1a. Kaplan Meier survival curves of Sorafenib treated patients versus control

Figure 1b. Kaplan Meier survival curves of patients with hepatic decompensation treated with Sorafenib versus control

Figure 1c. Propensity score adjusted Kaplan Meier survival curves Sorafenib treated patients versus control

Figure 2a. Kaplan Meier survival curves of Sorafenib treated patients stratified by presence of decompensation

Figure 2b. Decompensated Sorafenib treated patients stratified by the number of unique hepatic decompensation codes (ascites, hepatic encephalopathy, and esophageal varices) in Sorafenib treated patients

Figure 3a. Cost-effectiveness acceptability curve for sorafenib treatment in the overall sample. The dashed vertical line depicts the median, while the solid vertical line represents the $100,000 threshold

Figure 3b. Cost-effectiveness acceptability curve for sorafenib treatment in the propensity score matched sample. The dashed vertical line depicts the median, while the solid vertical line represents the $100,000 threshold

References

1. El-Serag HB. Hepatocellular carcinoma. New England Journal of Medicine 2011;365:1118-1127.
2. Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.
3. Bruix J, Sherman M. Management of Hepatocellular Carcinoma: An Update. Hepatology 2011;In Press.
4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, et al. Sorafenib in advanced hepatocellular carcinoma. The New England journal of medicine 2008;359:378-390.
5. LG DAF, Barroso-Sousa R, Bento AD, Blanco BP, Valente GL, Pfiffer TE, Hoff PM, et al. Safety and efficacy of sorafenib in patients with Child-Pugh B advanced hepatocellular carcinoma. Mol Clin Oncol 2015;3:793-796.
6. Lencioni R, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, et al. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. Int J Clin Pract 2014;68:609-617.
7. Kabiri M, Jazwinski AB, Roberts MS, Schaefer AJ, Chhatwal J. The changing burden of hepatitis C virus infection in the United States: model-based predictions. Annals of Internal Medicine 2014;161:170-180.
8. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40:IV-3-18.
9. Huskamp HA, Keating NL. The new medicare drug benefit: formularies and their potential effects on access to medications. J Gen Intern Med 2005;20:662-665.
10. Fritz AG. International classification of diseases for oncology : ICD-O. 3rd ed. Geneva: World Health Organization, 2000: vii, 240 p.
11. Artinyan A, Marshall CL, Balentine CJ, Albo D, Orcutt ST, Awad SS, Berger DH, et al. Clinical outcomes of oncologic gastrointestinal resections in patients with cirrhosis. Cancer 2012;118:3494-3500.
12. Yang JD, Kim WR, Coelho R, Mettler TA, Benson JT, Sanderson SO, Therneau TM, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9:64-70.
13. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 1998;54:948-963.
14. Hsu CY, Lee YH, Hsia CY, Huang YH, Su CW, Lin HC, Lee RC, et al. Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the Barcelona Clinic Liver Cancer system. Hepatology 2013;57:112-119.
15. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276:1339-1341.
16. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253-1258.
17. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004;7:518-528.
18. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. New England Journal of Medicine 2014;371:796-797.
19. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 1994;3:309-319.
20. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ 1998;7:723-740.

21. Ho DE, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. Journal of Statistical Software 2011;42.
22. Therneau T. A Package for Survival Analysis in S. In. 2.38 ed; 2015.
23. Hansen BB, Bowers J. Covariate balance in simple, stratified and clustered comparative studies. Statistical Science 2008;23:219-236.
24. Bowers J, Fredrickson M, Hansen B. RItools: Randomization Inference Tools. In. R package version 0.1-12 ed; 2014.
25. Harrell FE. rms: Regression Modeling Strategies. In. R package version 4.3-1 ed; 2015.
26. Fox J, Weisberg S. An R companion to applied regression. 2nd ed. Thousand Oaks, Calif.: SAGE Publications, 2011: xxii, 449 p.
27. R: A language and environment for statistical computing. In: R Foundation for Statistical Computing; 2015.
28. Lencioni R, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, et al. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. International Journal of Clinical Practice 2014;68:609-617.
29. Jorge A. Marrero RL, Sheng-Long Ye, Masatoshi Kudo, Jean-Pierre Bronowicki, Xiao-Ping Chen, Lucy Dagher, Junji Furuse, Jean-Francois Geschwind, Laura Ladrón de Guevara, Christos Papandreou, Arun J. Sanyal, Tadatoshi Takayama, Seung Kew Yoon, Keiko Nakajima, Alan Paul Venook. Final analysis of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma [HCC] and of Its Treatment with Sorafenib [Sor]) in >3000 Sor-treated patients (pts): Clinical findings in pts with liver dysfunction. In: Program and abstracts of the 49th Annual Meeting of the American Society of Clinical Oncology; 2013 May 31 - June 4, 2013; Chicago, IL; 2013.
30. Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. Clin Transl Gastroenterol 2014;5:e45.
31. Sorafenib in First-line Treatment of Advanced B Child Hepatocellular Carcinoma (BOOST). In. https://clinicaltrials.gov/ct2/show/NCT01405573.
32. Zhang P, Yang Y, Wen F, He X, Tang R, Du Z, Zhou J, et al. Cost-effectiveness of sorafenib as a first-line treatment for advanced hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2015;27:853-859.
33. Camma C, Cabibbo G, Petta S, Enea M, Iavarone M, Grieco A, Gasbarrini A, et al. Cost-effectiveness of sorafenib treatment in field practice for patients with hepatocellular carcinoma. Hepatology 2013;57:1046-1054.
34. Yopp AC, Mansour JC, Beg MS, Arenas J, Trimmer C, Reddick M, Pedrosa I, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. Ann Surg Oncol 2014;21:1287-1295.
35. Hartley D, Quam L, Lurie N. Urban and rural differences in health insurance and access to care. Journal of Rural Health 1994;10:98-108.
36. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of Hepatocellular Carcinoma Incidence in the United States Forecast Through 2030. Journal of Clinical Oncology 2016.

Table 1. Summary characteristic of the overall sample stratified by sorafenib treatment;

AJCC – American Joint Committee on Cancer

		Sorafenib	Control	P Value
		N=228	N=870	
Mean Age (SD)		69.5 ± 9.4	72.9 ± 9.7	<0.001
Gender	**Female (%)**	60 (26.3)	228 (26.2)	1.000
	Male (%)	168 (73.7)	642 (73.8)	
Race	**White (%)**	164 (71.9)	655 (75.3)	0.040
	Black (%)	22 (9.6)	109 (12.5)	
	Other (%)	42 (18.4)	106 (12.2)	
Stage	**Stage III (%)**	120 (52.6)	463 (53.2)	0.882
	Stage IV (%)	108 (47.4)	407 (46.8)	
Region	**Midwest (%)**	12 (5.3)	66 (7.6)	0.400
	Northeast (%)	24 (10.5)	112 (12.9)	
	South (%)	46 (20.2)	183 (21)	
	West (%)	146 (64)	509 (58.5)	
Urban setting (%)		158 (69.3)	597 (68.6)	0.873
Seen at a teaching center (%)		129 (56.6)	416 (47.8)	0.021
Seen at a National Cancer Institute designated center (%)		27 (11.8)	99 (11.4)	0.816
Seen at a		66 (28.9)	204 (23.4)	0.100

transplant center (%)				
Charlson comorbidity Index		0 ± 1.0	1 ± 2.0	<0.001
	0 (%)	127 (55.7)	382 (43.9)	0.002
	1 (%)	54 (23.7)	203 (23.3)	0.93
	2 (%)	23 (10.1)	130 (14.9)	0.067
	>3 (%)	24 (10.5)	155 (17.8)	0.009
Presence of hepatic decompensation (%)		81 (35.5)	341 (39.2)	0.312
	Hepatic encephalopathy (%)	23 (10.1)	119 (13.7)	0.183
	Esophageal varices (%)	21 (9.2)	100 (11.5)	0.405
	Ascites (%)	63 (27.6)	273 (31.4)	0.294

Table 2. Multivariate Predictors of mortality in the Overall Sample and in Propensity Matched Sample; AJCC – American Joint Committee on Cancer; MW - Midwest

	Overall Sample (n=1,098)			Propensity Matched Sample (n=456)		
	HR	**95% CI**	**p Value**	**HR**	**95% CI**	**p value**
Sorafenib treatment	0.66	0.57-0.77	<0.001	0.55	0.46-0.67	<0.001
AJCC Stage IV (vs. III)	1.40	1.24-1.58	<0.001	1.33	1.10-1.61	0.003
Urban setting	1.45	1.21-1.73	<0.001	1.94	1.40-2.68	<0.001
Seen at a teaching center	0.97	0.82-1.16	0.75	0.81	0.59-1.12	0.21
Seen at a National Cancer Institute designated center	0.77	0.62-0.97	0.024	0.77	0.54-1.11	0.16
Seen at a transplant center	0.77	0.65-0.93	<0.001	0.74	0.56-0.99	0.045
Charlson Comorbidity Index	1.00	0.96-1.04	0.88	1.01	0.93-1.09	0.85
Age	1.01	1.00-1.01	0.14	1.01	1.00-1.02	0.038
Presence of hepatic decompensation	1.49	1.30-1.70	<0.001	1.74	1.40-2.16	<0.001
Northeast (vs. MW)	1.08	0.80-1.46	0.60	1.38	0.83-2.29	0.22
South (vs. MW)	0.98	0.75-1.29	0.90	0.86	0.53-1.40	0.55
West (vs. MW)	0.98	0.75-1.28	0.88	0.93	0.60-1.46	0.76
Male gender	1.01	0.88-1.17	0.85	1.00	0.80-1.25	0.99
Black (vs. White)	1.20	0.98-1.48	0.086	1.21	0.77-1.91	0.40
Other (vs. White)	1.14	0.95-1.38	0.17	0.97	0.66-1.41	0.85

Table 3. Multivariate Predictors of Survival in Patients with hepatic decompensation (n=422); AJCC – American Joint Committee on Cancer; MW - Midwest

	HR	95% CI	p value
Sorafenib treatment	0.61	0.47-0.79	<0.001
AJCC Stage IV (vs. III)	1.27	1.04-1.56	0.0203
Urban setting	1.57	1.14-2.16	0.0061
Seen at a teaching center	0.98	0.76-1.28	0.8895
Seen at a National Cancer Institute designated center	0.62	0.45-0.86	0.004
Seen at a transplant center	0.81	0.63-1.06	0.12
Charlson Comorbidity Index	0.98	0.93-1.03	0.48
Age	1.00	0.99-1.01	0.45
Northeast (vs. MW)	1.03	0.64-1.68	0.89
South (vs. MW)	0.86	0.54-1.38	0.53
West (vs. MW)	0.91	0.57-1.45	0.69
Male	1.06	0.85-1.34	0.59
Black (vs. White)	1.01	0.71-1.43	0.97
Other (vs. White)	1.18	0.87-1.62	0.29

Table 4. Sensitivity Analysis of ECOG score- Multivariate hazard with 95% confidence interval with different distributions of ECOG 3-4 status in treated and control patients.

Light gray shading indicates significant survival benefit associated with sorafenib therapy;

ECOG - Eastern Cooperative Oncology Group

Hazard of ECOG 3-4: 1.5		Prevalence of ECOG 3-4 for Sorafenib Treated Patients					
		0	0.1	0.2	0.3	0.4	0.5
Prevalence of ECOG 3-4 for Control Patients	0	0.67 (0.57, 0.78)	0.62 (0.52, 0.73)	0.57 (0.47, 0.68)	0.53 (0.43, 0.64)	0.49 (0.39, 0.6)	0.45 (0.35, 0.56)
	0.1	0.72 (0.62, 0.83)	0.67 (0.57, 0.78)	0.62 (0.52, 0.73)	0.58 (0.48, 0.69)	0.54 (0.44, 0.65)	0.5 (0.4, 0.61)
	0.2	0.77 (0.67, 0.88)	0.72 (0.62, 0.83)	0.67 (0.57, 0.78)	0.63 (0.53, 0.74)	0.58 (0.48, 0.69)	0.54 (0.44, 0.65)
	0.3	0.81 (0.71, 0.92)	0.76 (0.66, 0.87)	0.71 (0.61, 0.82)	0.67 (0.57, 0.78)	0.63 (0.53, 0.74)	0.59 (0.49, 0.7)
	0.4	0.85 (0.75, 0.96)	0.8 (0.7, 0.91)	0.76 (0.66, 0.87)	0.71 (0.61, 0.82)	0.67 (0.57, 0.78)	0.63 (0.53, 0.74)
	0.5	0.89 (0.79, 1)	0.84 (0.74, 0.95)	0.8 (0.7, 0.91)	0.75 (0.65, 0.86)	0.71 (0.61, 0.82)	0.67 (0.57, 0.78)
	0.6	0.93 (0.83, 1.04)	0.88 (0.78, 0.99)	0.84 (0.74, 0.95)	0.79 (0.69, 0.9)	0.75 (0.65, 0.86)	0.71 (0.61, 0.82)
	0.7	0.97 (0.87, 1.08)	0.92 (0.82, 1.03)	0.87 (0.77, 0.98)	0.83 (0.73, 0.94)	0.79 (0.69, 0.9)	0.75 (0.65, 0.86)
	0.8	1.01 (0.91, 1.12)	0.96 (0.86, 1.07)	0.91 (0.81, 1.02)	0.87 (0.77, 0.98)	0.82 (0.72, 0.93)	0.78 (0.68, 0.89)
	0.9	1.04 (0.94, 1.15)	0.99 (0.89, 1.1)	0.95 (0.85, 1.06)	0.9 (0.8, 1.01)	0.86 (0.76, 0.97)	0.82 (0.72, 0.93)
	1	1.08 (0.98, 1.19)	1.03 (0.93, 1.14)	0.98 (0.88, 1.09)	0.94 (0.84, 1.05)	0.89 (0.79, 1)	0.85 (0.75, 0.96)

Table 5. Cost effectiveness of sorafenib treatment in the overall sample, propensity score subsets, and in patients with hepatic decompensation in USD (2015); ICER – incremental cost-effectiveness ratio

	Overall		Overall Sample Propensity Score Matched		Decompensated		Decompensated Propensity Score Matched	
	Control	Sorafenib	Control Propensity	Sorafenib Propensity	Control	Sorafenib	Control Propensity	Sorafenib Propensity
Outpatient (SD)	4562 (7821)	6289 (7029)	4585 (8743)	6289 (7029)	3902 (4082)	5387 (5868)	4198 (4076)	5387 (5868)
Inpatient (SD)	16182 (16955)	17028 (21855)	16020 (16816)	17028 (21855)	19515 (17775)	20238 (24278)	19572 (18157)	20238 (24278)
Medications (SD)	1492 (5037)	17734 (23477)	2264 (8824)	17734 (23477)	1512 (2173)	16429 (20801)	753 (1027)	16429 (20801)
Total (SD)	10950 (19507)	31364 (33957)	11678 (20292)	31364 (33957)	13922 (18997)	32519 (36066)	16557 (19537)	32519 (36066)
Mean cost	10950	31364	11678	31364	13922	32519	16557	32519
Median survival	0.17	0.41	0.17	0.41	.17	.25	.17	.25
ICER	84250		81249		224914		188065	

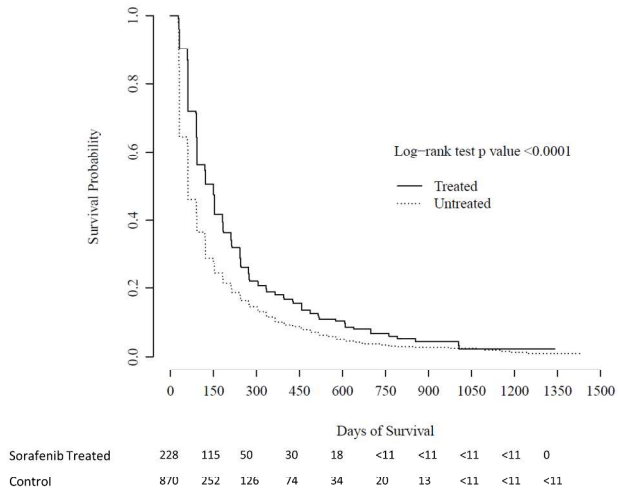

Figure 1

Figure 1a. Kaplan Meier survival curves of Sorafenib treated patients versus control

254x190mm (300 x 300 DPI)

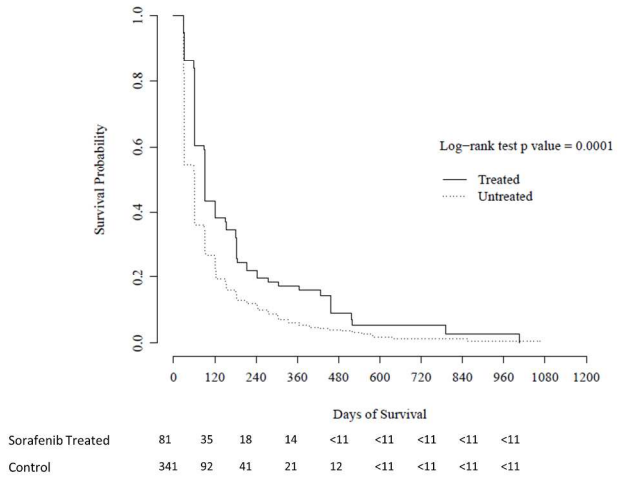

Figure 1b

Figure 1b. Kaplan Meier survival curves of patients with hepatic decompensation treated with Sorafenib versus control

254x190mm (300 x 300 DPI)

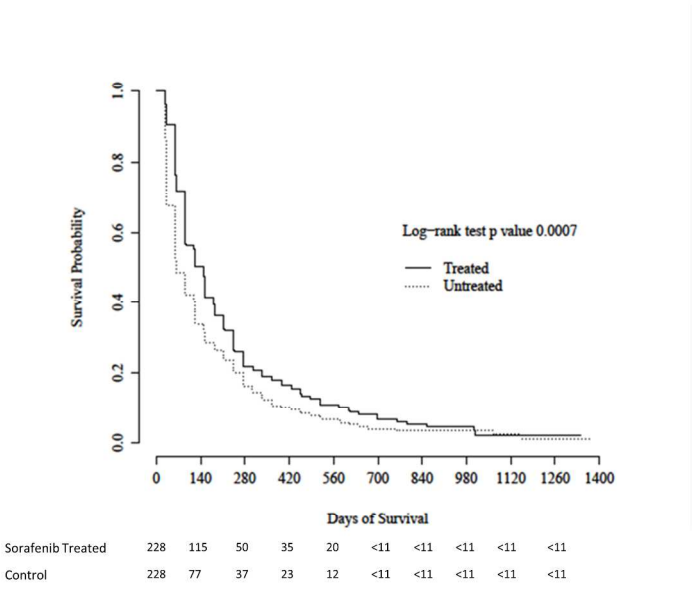

Figure 1c

Figure 1c. Propensity score adjusted Kaplan Meier survival curves Sorafenib treated patients versus control

254x190mm (300 x 300 DPI)

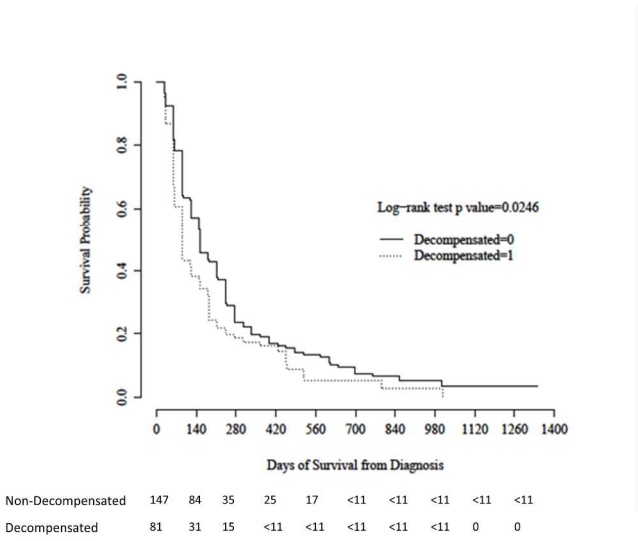

Figure 2a

Figure 2a. Kaplan Meier survival curves of Sorafenib treated patients stratified by presence of decompensation

254x190mm (300 x 300 DPI)

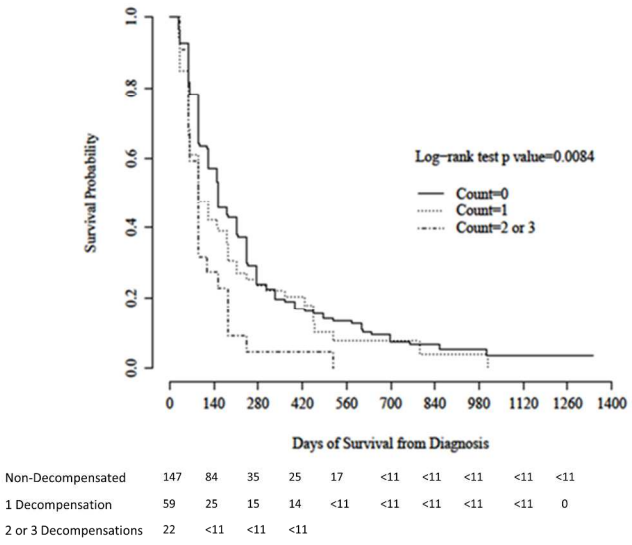

Figure 2b

Figure 2b. Decompensated Sorafenib treated patients stratified by the number of unique hepatic decompensation codes (ascites, hepatic encephalopathy, and esophageal varices) in Sorafenib treated patients

254x190mm (300 x 300 DPI)

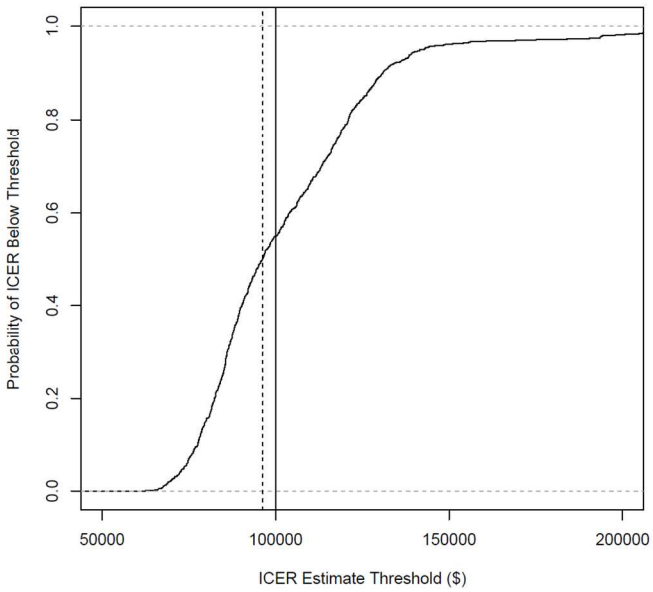

Figure 3a

Figure 3a. Cost-effectiveness acceptability curve for sorafenib treatment in the overall sample. The dashed vertical line depicts the median, while the solid vertical line represents the $100,000 threshold

254x190mm (300 x 300 DPI)

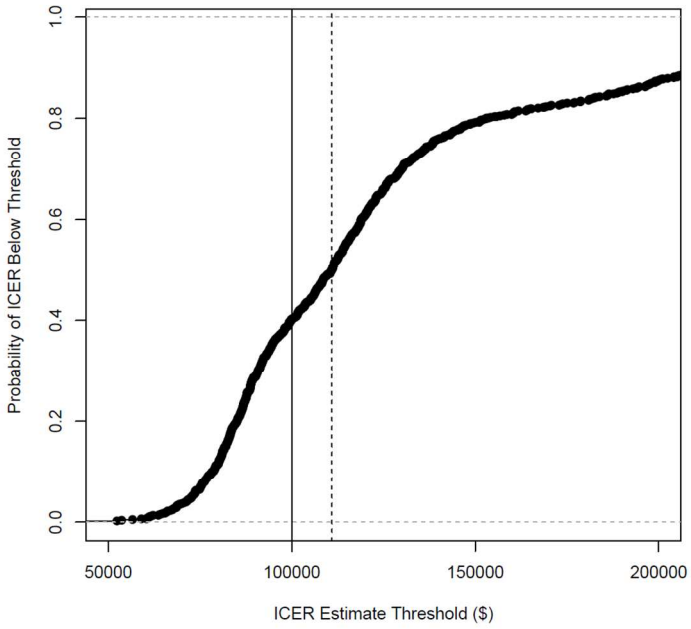

Figure 3b

Figure 3b. Cost-effectiveness acceptability curve for sorafenib treatment in the propensity score matched sample. The dashed vertical line depicts the median, while the solid vertical line represents the $100,000 threshold

254x190mm (300 x 300 DPI)

Supplemental Table 1. Multivariate Predictors of Survival in Propensity Matched Decompensated Patients (n=162); AJCC – American Joint Committee on Cancer; MW - Midwest

	HR	95% CI	p value
Sorafenib	0.62	0.45-0.87	0.006
AJCC Stage IV (vs. III)	1.48	1.05-2.08	0.027
Urban setting	1.42	0.82-2.47	0.21
Seen at a teaching center	1.53	0.97-2.41	0.067
Seen at a National Cancer Institute designated center	0.75	0.46-1.23	0.25
Seen at a transplant center	0.59	0.38-0.92	0.019
Charlson Comorbidity Index	0.94	0.83-1.08	0.38
Age	1.00	0.98-1.01	0.54
Northeast (vs. MW)	1.46	0.57-3.77	0.43
South (vs. MW)	1.55	0.63-3.81	0.34
West (vs. MW)	1.83	0.77-4.36	0.17
Male gender	1.01	0.71-1.45	0.95
Black (vs. White)	0.93	0.51-1.69	0.80
Other (vs. White)	1.27	0.75-2.17	0.38

Supplemental Table 2. Multivariate Predictors of Survival in Sorafenib Treated Patient (n=228); AJCC – American Joint Committee on Cancer; MW - Midwest

	HR	95% CI	p value
AJCC Stage IV (vs. III)	1.23	0.93-1.62	0.15
Urban setting	2.12	1.32-3.41	0.002
Seen at a teaching center	0.72	0.46-1.14	0.16
Seen at a National Cancer Institute designated center	0.91	0.53-1.54	0.72
Seen at a transplant center	0.88	0.58-1.33	0.54
Charlson Comorbidity Index	1.03	0.92-1.16	0.59
Age	0.99	0.98-1.01	0.35
Presence of hepatic decompensation	1.29	0.94-1.76	0.11
Northeast (vs. MW)	1.59	0.75-3.33	0.22
South (vs. MW)	1.09	0.54-2.19	0.81
West (vs. MW)	1.14	0.59-2.20	0.69
Male gender	1.15	0.83-1.61	0.40
Black (vs. White)	1.13	0.69-1.85	0.64
Other (vs. White)	1.15	0.77-1.70	0.50

Supplemental Table 3. Sensitivity Analysis of ECOG score- Multivariate hazard with 95% confidence interval with different distributions of ECOG 3-4 status in treated and control patients. Light gray shading indicates significant survival benefit associated with sorafenib therapy. Dark gray shading indicates a significantly worse survival associated with sorafenib therapy.

Hazard of ECOG 3-4: 2.0		Prevalence of ECOG 3-4 for Sorafenib Treated Patients					
		0	0.1	0.2	0.3	0.4	0.5
Prevalence of ECOG 3-4 for Control Patients	0	0.67 (0.57, 0.78)	0.57 (0.47, 0.68)	0.49 (0.39, 0.6)	0.41 (0.31, 0.52)	0.33 (0.23, 0.44)	0.26 (0.16, 0.37)
	0.1	0.77 (0.67, 0.88)	0.67 (0.57, 0.78)	0.58 (0.48, 0.69)	0.5 (0.4, 0.61)	0.43 (0.33, 0.54)	0.36 (0.26, 0.47)
	0.2	0.85 (0.75, 0.96)	0.76 (0.66, 0.87)	0.67 (0.57, 0.78)	0.59 (0.49, 0.7)	0.52 (0.42, 0.63)	0.45 (0.35, 0.56)
	0.3	0.93 (0.83, 1.04)	0.84 (0.74, 0.95)	0.75 (0.65, 0.86)	0.67 (0.57, 0.78)	0.6 (0.5, 0.71)	0.53 (0.43, 0.64)
	0.4	1.01 (0.91, 1.12)	0.91 (0.81, 1.02)	0.82 (0.72, 0.93)	0.74 (0.64, 0.85)	0.67 (0.57, 0.78)	0.6 (0.5, 0.71)
	0.5	1.08 (0.98, 1.19)	0.98 (0.88, 1.09)	0.89 (0.79, 1)	0.81 (0.71, 0.92)	0.74 (0.64, 0.85)	0.67 (0.57, 0.78)
	0.6	1.14 (1.04, 1.25)	1.04 (0.94, 1.15)	0.96 (0.86, 1.07)	0.88 (0.78, 0.99)	0.8 (0.7, 0.91)	0.73 (0.63, 0.84)
	0.7	1.2 (1.1, 1.31)	1.11 (1.01, 1.22)	1.02 (0.92, 1.13)	0.94 (0.84, 1.05)	0.86 (0.76, 0.97)	0.8 (0.7, 0.91)
	0.8	1.26 (1.16, 1.37)	1.16 (1.06, 1.27)	1.08 (0.98, 1.19)	1 (0.9, 1.11)	0.92 (0.82, 1.03)	0.85 (0.75, 0.96)
	0.9	1.31 (1.21, 1.42)	1.22 (1.12, 1.33)	1.13 (1.03, 1.24)	1.05 (0.95, 1.16)	0.98 (0.88, 1.09)	0.91 (0.81, 1.02)
	1	1.36 (1.26, 1.47)	1.27 (1.17, 1.38)	1.18 (1.08, 1.29)	1.1 (1.0, 1.21)	1.03 (0.93, 1.14)	0.96 (0.86, 1.07)