**Sorafenib for the treatment of advanced hepatocellular cancer – a United Kingdom audit**

J King1, D Palmer2,3, P Johnson2,3, P Ross4, RA Hubner5, J Graham6, S Darby7, C Braconi8, C Iwuji9, D Swinson10, P Collins11, K Patel12 J Nobes13, I Muazzam14, C Blesing15, A Kirkwood 16, S Nash16, T Meyer1, 17

1 Department of Oncology, Royal Free London  NHS Foundation Trust; 2University of Birmingham; 3 University of Liverpool; 4 King’s College Hospital, London; 5The Christie NHS Foundation Trust; 6 The Newcastle upon Tyne NHS Foundation Trust; 7 Sheffield Teaching Hospitals NHS Foundation Trust; 8 University of Glasgow; Beatson West of Scotland Cancer Centre, Glasgow; 9Leicester Royal Infirmary; 10 Leeds Teaching Hospitals NHS Trust; 11 University Hospitals Bristol NHS Foundation Trust; 12 Oxford University Hospitals NHS Trust;13 Norfolk and Norwich University Hospitals NHS Foundation Trust; 14 Hull and East Yorkshire Hospitals NHS Trust; 15 Great Western Hospital NHS Trust, Swindon; 16 Cancer Research UK & UCL Cancer Trials Centre, London; 17 UCL Cancer Institute, London

Address for correspondence

Prof Tim Meyer

UCL Cancer Institute

University College London

72 Huntley Street, London WC1E 6BT

email; t.meyer@ucl.ac.uk Tel; 0207 679 6731, Fax; 0203 108 2025

Word count xx/6000; x figures and tables

List of Abbreviations:

Key Words:

Conflict of Interest:

Financial support:

Author contributions: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; administrative, technical, or material support; study supervision)

**Abstract** 243/250

Background and Aims: Sorafenib is the current standard treatment for advanced hepatocellular carcinoma (HCC). We performed a national audit of UK patients treated with sorafenib as standard of care or systemic therapy within first-line trials.

Method: Sorafenib-treated (ST) and trial-treated (TT) patients were identified via the Cancer Drugs Fund and local data bases. Data was collected retrospectively from medical and pharmacy records according to a standard case report form. The primary outcome was median overall survival (OS), estimated by the Kaplan-Meier method.

Results: Data was obtained for 448 ST patients from 15 hospitals. The median age was 68 years (range 17-89) and 75% had a performance status (PS) of ≤1. At baseline, 77% were Child-Pugh (CP)-A and 16.1% CP-B, 38% were ALBI-1 and 48% ALBI-2, 23% were BCLC-B and 72% BCLC-C.Median time on sorafenib was 3.6 months with a mean daily dose of 590mg. Median OS for 448 evaluable ST patients (342 events) was 8.5 months. There were significant differences in OS comparing; CP-A vs CP-B, (9.5 vs 4.6 months), ALBI-1 vs ALBI-2, (12.9 vs 5.9 months) and BCLC-B vs BCLC (13.0 vs 8.3 months). For TT patients (n=109), the median OS was 8.1 months and this was not significantly different from the ST treated patients.

Conclusion: Despite treatment, survival for advanced HCC remains poor, particularly in those with impaired liver function as assessed by CP or ALBI grade. More effective therapies and careful patient selection are required to improve outcomes.

.

**Introduction**

Hepatocellular carcinoma (HCC) is the second most common cause of cancer death world-wide and accounted for 746,000 deaths in 2012 (1). In England, liver cancer incidence has increased by 70% for males and 60% for females from 2003 between 2012 and is now the 18th most common cancer with an annual incidence of almost 4000 per year (Office of National Statistics). Overall, the prognosis is poor and the 5-year age-standardised net survival for adults with liver cancer in the UK is 9.3% (2). The mainstay of curative treatment is surgical resection or transplantation but the majority of patients are not suitable due to underlying liver dysfunction or because the disease is too advanced at presentation. For patients with liver-confined disease, loco-regional therapies may be applicable but for those with advanced disease, palliative systemic therapy and supportive are care required. To date, sorafenib remains the only drug licenced for the systemic treatment of HCC based on the results of two randomised clinical trials which demonstrated an improvement in median overall survival of between 2-3 months compared with placebo (3, 4). The largest trial was the SHARP trial which was conducted mainly in Northern America and Europe, including the UK, and recruited 602 patients of which 299 were randomised to placebo. Among these, the majority (95%) had well preserved liver function with Child-Pugh A liver disease and good ECOG performance status <2 (92%), and the median survival was 10.7 months compared with 7.9 months in the placebo group (HR 0.69 (0.55–0.87) <0.001). On this basis, sorafenib was approved for HCC by the European Agency for the Evaluation of Medicinal Products (EMA) in 2007 and is recommended in international guidelines (5).

The National Institute for Clinical Excellence (NICE) and Scottish Medicines Consortium (SMC) both published guidance in 2010 and recommended against the use of sorafenib for advanced HCC on the basis cost-effectiveness. However, in England, the Cancer Drug Fund (CDF) which was established in April 2011, has provided funding for sorafenib as first-line therapy for patients with advanced HCC with Child-Pugh A liver impairment or Child-Pugh grade B liver impairment with low disease burden. Until the introduction of the CDF, selected patients were able to receive sorafenib based on individual applications to the local health funding authorities.

The clinicopathological characteristics and clinical outcome of patients with advanced HCC treated in the UK has not been previously reported and we therefore undertook a retrospective national audit to define; the patient population treated with sorafenib in the UK, the outcome in terms of overall survival, and to compare the outcomes between those treated within and out-with first line clinical trials.

**Patients and Methods**:

This was an investigator-initiated collaborative study without industry support. All UK centres that treat HCC were identified via the UK database of cancer networks, through which cancer care is geographically coordinated in the UK. The Patient Advice and Liaison office for each Hospital Trust provided contact details for all clinicians who managed patients with HCC, and they were invited to participate in in the study. For each hospital, HCC patients who had received sorafenib as first line systemic therapy were identified via local Cancer Drugs Fund records or locally held databases. Only patients treated within the NHS were included. In addition, we identified first-line drug trials for HCC that were recruiting in UK during the study period. Anonymised clinical and treatment data were collected from medical and pharmacy records according to a study-specific case report form. In addition to baseline clinicopathological data, we also collected data on administered daily dose and duration of treatment. Although toxicity was not recorded according to CTC grade, we recorded the adverse events that resulted in dose reduction, interruption or termination of treatment and thereby captured toxicity of clinical relevance to patient management. The primary outcome measure was overall survival (OS). Ethics approval was granted for this research (REC reference 12/LO/1088).

Statistics

Analyses were performed using Stata version 12.1. OS was estimated using Kaplan-Meier methods from commencement of sorafenib to date of death or to date of last follow-up. Cox proportional hazards regression analysis was used to obtain univariate hazard ratios. All variables in Table 1 were considered for inclusion in the multivariable model, except where there was co-linearity with existing variables or where there was greater than 10% missing data. Continuous variables were analysed as categorical variables, with the cut-offs decided as: upper limit of normal range for albumin and bilirubin, and median average value for AFP. ECOG performance status (PS) was included as a categorical variable with three levels (0; 1; 2 or 3). Baseline variables which were associated with the overall survival in a univariable Cox model (p<0.1) were included in the multivariable model. Kaplan-Meier estimated survival curves were used to compare sorafenib and trial-treated patients, and the effect of Child-Pugh (CP) grade, albumin-bilirubin (ALBI) grade (6) and BCLC stage (7) amongst sorafenib patients. The mean daily dose of sorafenib was calculated by establishing the mean daily dose per patient during the course of their treatment and establishing the median mean dose for the whole population.

**Results**:

*Sorafenib treated (ST) patients*

Data was obtained for 448 ST patients from 15 hospitals, who were commenced on sorafenib from 1st July 2007 to 24th July 2013. Most of the major liver cancer centres participated and patients received sorafenib under the supervision of an oncologist in 14 out of 15 hospitals and a hepatologist in one. The number of patients treated with sorafenib per institution ranged from 4 to 125. Baseline characteristics are shown in Table 1. The median age was 68 years (range 17-89) with a male: female ratio of 4.9:1. The majority of patients were ECOG PS ≤ 1 (75%), 77% were CP-A and 73% BCLC-C. Extra-hepatic disease or vascular invasion was reported in 38% and 20% respectively although there was a high rate of missing data for vascular invasion. The most common single aetiology was alcohol in 25% and a high proportion (42%) had previously received prior local therapy for HCC, of whom 74% had undergone trans-arterial (chemo) embolisation and 12% had received radiofrequency ablation (RFA).

*Treatment dose and toxicity*

Full treatment data were available for 436 patients. The median time on sorafenib treatment was 3.6 months (range x-y), with a mean daily sorafenib dose of 590mg. Overall, 271 (62%) started at 800mg daily, 143 (33%) started at 400mg daily and the remainder started at 200mg (4%) or 600mg (1%) daily. A dose reduction was required in 140 (52%) patients, and 84 (31%) had their treatment temporarily interrupted due to toxicity. The main toxicities leading to a dose reduction or treatment interruption are shown in Table 2. Fatigue, deterioration in PS and diarrhoea were the most common listed. Interestingly, the frequency of adverse events was similar for CP-A and CP-B patients with the exception of liver dysfunction which was more common in those with CP-B disease: 18% vs 40% for CP A vs B, respectively. The reason sorafenib was discontinued was known for 336 patients, of whom 98 (29%) had progressed radiologically, 84 (25%) stopped due to toxicity, 63 (19%) had progressed clinically and 65 (19%) died.

*Efficacy*

The median OS for 448 evaluable ST patients (342 events) was 8.5 months. In the univariate analysis, a significantly decreased risk of death was seen in patients with ECOG PS 0, those who had undergone previous local therapy, those with a baseline albumin of ≥ 36g/L, bilirubin <17μmol/L, , AFP <400ng/ml and those without vascular invasion (Table 3). In the multivariate analysis, the independent predictors of mortality were: performance status, previous local therapy, bilirubin, albumin and AFP. Vascular invasion was omitted due to high proportion of missing data. CP grade, ALBI grade and BCLC stage and scores were included in univariate analysis, but omitted from the multivariate analysis due to their co-linearity with albumin, bilirubin or PS. There were significant differences in survival between patients with CP-A (n=343) vs CP-B (n=72); 9.5 vs 4.6 months (Figure 1A). The albumin-bilirubin (ALBI) grade has recently been described as an alternative to CP as an objective measures of liver function that can independently influence survival in patients with HCC (8). For patients with ALBI-1 (n=168) vs ALBI-2 (n=214), the median survival was 12.9 vs 5.9 months (Figure 1B). For BCLC B (n=104) vs C (n=322), the median survival was 13.0 vs 8.3 months (Figure 1C). Comparing these three composite scores, ALBI gave rise to the highest hazard ratio (Table 3)

Trial treated (TT) patients

Data was collected on 109 TT patients who were recruited to five first line trials for advanced HCC in five of the contributing hospitals. Details of the study and recruitment are given in Table 4. The baseline characteristics are listed in Table 1 and, compared to the ST cohort; the TT cohort tended to have a higher proportion of ECOG PS 0 and CP A patients, but also had a greater proportion with vascular involvement and extra-hepatic disease. The median time on trial drug was 3.7 months (range x-y). Median OS was 8.1 months for 109 TT patients (91 events). There was no difference in survival between ST vs TT patients: unadjusted HR = 0.95 (95%CI 0.71-1.20), p=0.69 (Figure 1D).

**Discussion:**

Further to the data obtained from randomised clinical trials, observational studies provide important additional information on the efficacy and toxicity of therapy when applied to a larger and more diverse population which is distinct from the highly selected trial population (9). Moreover, for the treatment of hepatocellular carcinoma, where geographical and aetiological differences result in profound differences in outcome (10), it is important to understand the relevance of a global trial such as the SHARP trial to the local population. The UK data presented here shows that median OS survival of ST patients in the UK was inferior to that reported in the SHARP study and this is likely to be a result of differences in baseline characteristics. An exploratory multivariate analysis within the SHARP trial identified, among other factors, ECOG PS and CP status as having a significant impact on survival (3). In SHARP, 54% were PS 0 and 95% CP A compared with 26% and 77% respectively in our study. In a sub-analysis of SHARP, those with a PS of 0 had an OS of 13.3 months compared to 8.9 months for those with PS 1-2 illustrating the relevance of PS to OS (11). In subsequent global, randomised trials in which sorafenib has been used as the control arm, the reported OS for sorafenib treated patients has ranged from 8.5 to 10.2 months (12-15). Recruitment to many of these trials was ongoing in the UK and approximately 20% of UK patient receiving systemic therapy went into first line trials. We therefore included these patients in a parallel analysis to explore the possibility that the exclusion of these patients from routine care biased the study. Surprisingly, we found no difference in median OS between the trial and non-trial treated cohorts. However, the imbalance between the treatments received and some baseline characteristics prevents further interpretation of this observation.

There are few large, multicentre observational studies with which to compare our data. An Italian collaborative study group (SOFIA) has published a field-practice study including prospective data from 296 patients from six centres and reported a median OS of 10.5 months; 8.5 months in BCLC-C and 20.6 months in BCLC-B (16). In this study 56% had PS0 and 88% were CP A so were more comparable with SHARP. Additionally, 51% had hepatitis C only has a cause of chronic liver disease compared with 16% in our population. Hepatitis C has been proposed as a positive predictive factor for survival with sorafenib (11) although we did not confirm this in our study by univariate analysis. In common with both SHARP and the SOFIA study group study, we show that ECOG PS, bilirubin and albumin are significant independent predictors of survival for patients treated with sorafenib. Another multicentre retrospective study from Austria has also been reported including 148 patients from 11 institutions (17). Median OS was 7.4 months but only 52% were CP-A, and CP score was a significant prognostic factor in multivariate analysis. This raises the question to what extent those with impaired liver function benefit from sorafenib. Since all large randomised trials including sorafenib for HCC have excluded CP-B patients, information regarding toxicity and efficacy is predominantly available from other sources. The GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) study is an industry sponsored global non-interventional study designed primarily to assess safety of sorafenib in the real life population (18). The first interim analysis included 479 patients of which 143 were European and demonstrated that overall, 28% of those treated had CP B disease. While they reported similar toxicity comparing patients with CP A and B, they did not provide a breakdown by specific toxicity and it was noted that sorafenib was discontinued due to toxicity in 40% CP B patients compared with 25% CP A patients. Here, we show that deterioration in PS and liver function was more frequent in CP B patients as has also been reported in a small German study (19). Moreover, compared with CP A, the survival in patients with CP B disease was significantly worse at 4.6 months. The inferior survival of CP B patients treated with sorafenib has been shown in other studies and ranges from 2.0-7.7months and the appropriate stratification of patients according to liver function is therefore of key importance (16, 19-23). Recently, the ALBI grade has been developed and proposed as an alternative to CP method to assess liver function in patients with HCC (6). The ALBI grade is based only on albumin and bilirubin measured as continuous variables, and avoids the inherent subjectivity of some elements of CP score. As part of its validation, the ALBI grade was evaluated in 1,132 patients receiving sorafenib on clinical trials of which 96% were CP-A. Our analysis presented an opportunity to evaluate the ALBI grade in sorafenib-treated patients outside clinical trials and compare with CP grade. Interestingly we found that survival of patients with ALBI grade 1 was very similar comparing our cohort (12.9 months) with ALBI 1 trial cohort (12.7 months). For the ALBI 2 grade, the survival for our cohort was worse at 5.9 months compared with 7.2 months in the trial cohort which presumably reflects the inclusion of more CP B patients in our ALBI 2 cohort. Only 14 patients were categorised in the worst prognostic group and therefore it was not possible to estimate their survival with confidence. The ALBI score may therefore provide a useful method of stratification in trials which are predominantly CP A and help with prognostication in the clinic. However CP seems to provide information to help select those with a particularly poor outlook that may not benefit from sorafenib.

The main limitations of our study were that it was retrospective and there was a high proportion of missing data for some data fields. To minimise the impact of this, we chose a robust OS primary endpoint which had been met in 76% cases at the time of analysis. Moreover, for most of the key prognostic variables, with the exception of vascular invasion, data was available in around 90% cases. Toxicity was not recorded according to CTC criteria however we were able capture clinically relevant toxicity that resulted in dose reductions, interruption or termination of therapy. Finally, in the absence of an untreated control group, it is difficult to evaluate the absolute benefit of sorafenib in the UK population. However previously published data from UK patients deemed suitable for sorafenib but for whom funding was denied suggests a median OS of 4.1 months (24).

In summary our large collaborative study provides the first comprehensive survey of sorafenib use for HCC in the UK. We have defined the patient population in which it has been used, the outcome in terms of survival and associated prognostic variable. More generally, we show that patients treated within recent randomised trials have no better nor worse than those treated with sorafenib outside trials, but those with CP disease appear to derive little benefit. Finally, we provide the first external validation of the ALBI grade in patients with advanced HCC treated with sorafenib.

**Acknowledgements**

Table 1: baseline demographic and clinical characteristics of HCC patients who received sorafenib as first line systemic therapy or were treated first line on clinical trials

|  |  |  |
| --- | --- | --- |
|  | **Observational (N=448)** | **Trial (N=109)** |
| **Age at entry; median (range)** | 68 (17.0 - 89.0) | 68 (26.0 - 85.0) |
| **Sex** |  |  |
| Male | 325 (72.5%) | 87 (79.8%) |
| Female | 66 (14.7%) | 13 (11.9%) |
| No data | 57 (12.7%) | 9 (8.3%) |
| **Extra-hepatic disease** |  |  |
| No | 269 (60.0%) | 42 (38.5%) |
| Yes | 172 (38.4%) | 61 (56.0%) |
| No data | 7 (1.6%) | 6 (5.5%) |
| **ECOG PS** |  |  |
| 0 | 117 (26.1%) | 48 (44.0%) |
| 1 | 218 (48.7%) | 58 (53.2%) |
| 2 | 94 (21.0%) | 3 (2.8%) |
| 3 | 6 (1.3%) | - |
| No data | 13 (2.9%) | - |
| **Previous local therapy** |  |  |
| No | 258 (57.6%) | 52 (47.7%) |
| Yes | 190 (42.4%) | 57 (52.3%) |
| **Vascular invasion** |  |  |
| No | 161 (35.9%) | 58 (53.2%) |
| Yes | 91 (20.3%) | 36 (33.0%) |
| No data | 196 (43.8%) | 15 (13.8%) |
| **Bilirubin (µmol/L)** |  |  |
| < 17 | 238 (53.1%) | 68 (62.4%) |
| ≥ 17 | 158 (35.3%) | 36 (33.0%) |
| No data | 52 (11.6%) | 5 (4.6%) |
| **Albumin (g/L)** |  |  |
| < 36 | 121 (27.0%) | 29 (26.6%) |
| ≥ 36 | 276 (61.6%) | 75 (68.8%) |
| No data | 51 (11.4%) | 5 (4.6%) |
| **Hepatitis B** |  |  |
| No | 393 (87.7%) | 96 (88.1%) |
| Yes | 55 (12.3%) | 13 (11.9%) |
| **Hepatitis C** |  |  |
| No | 378 (84.4%) | 97 (89.0%) |
| Yes | 70 (15.6%) | 12 (11.0%) |
| **Alcohol** |  |  |
| No | 338 (75.4%) | 92 (84.4%) |
| Yes | 110 (24.6%) | 17 (15.6%) |
| **Child Pugh** |  |  |
| A | 343 (76.6%) | 100 (91.7%) |
| B | 72 (16.1%) | 7 (6.4%) |
| C | 2 (0.4%) | - |
| No data | 31 (6.9%) | 2 (1.8%) |
| **ALBI grade** |  |  |
| 1 | 168 (37.5%) | - |
| 2 | 214 (47.8%) | - |
| 3 | 14 (3.1%) | - |
| No data | 52 (11.6%) | 109 (100.0%) |
| **AFP (ng/ml)** |  |  |
| <400 | 227 (50.7%) | 51 (46.8%) |
| ≥400 | 141 (31.5%) | 51 (46.8%) |
| No data | 80 (17.9%) | 7 (6.4%) |
| **BCLC** |  |  |
| A | 3 (0.7%) | 1 (0.9%) |
| B | 104 (23.2%) | 11 (10.1%) |
| C | 322 (71.9%) | 95 (87.2%) |
| No data | 19 (4.2%) | 2 (1.8%) |

Abbreviations - ST: sorafenib treated; TT: trial treated; ECOG PS: Eastern Cooperative Group Performance Status; ALBI: albumin-bilirubin score; AFP: alphafetoprotein; BCLC: Barcelona Clinic Liver Cancer stage classification

Table 2: Adverse events leading to a dose reduction or treatment interruption for ST patients

|  |  |  |  |
| --- | --- | --- | --- |
|  | Overall %  n=224 | CP-A %  n=181 | CP-B %  n=43 |
| Fatigue | 45 | 45 | 47 |
| PS | 33 | 32 | 47 |
| Diarrhoea | 32 | 33 | 30 |
| Rash | 24 | 23 | 33 |
| Liver Function | 22 | 18 | 40 |
| Nausea | 12 | 12 | 16 |
| Weight Loss | 9 | 10 | 5 |
| Gastrointestinal bleed | 7 | 7 | 5 |
| Myelosuppression | 5 | 6 | 2 |
| Other | 17 | 17 | 21 |

CP: Child Pugh; PS: drop in performance status; Liver Function (bilirubin or transaminases)

Table 3: Risk factors for overall mortality in HCC patients treated with sorafenib

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | | **Univariable** | | **Multivariable\*** | |
| **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| ECOG PS | 0 | - | 0.008 | - | 0.055 |
| 1 | 1.45 (1.11 - 1.88) | 1.41 (1.05 - 1.89) |
| 2 or 3 | 1.54 (1.13 - 2.11) | 1.39 (0.98 - 1.97) |
| Previous local therapy | No | - | 0.004 | - | 0.023 |
| Yes | 0.73 (0.58 - 0.90) | 0.74 (0.58 - 0.96) |
| Bilirubin µmol/L | < 17 | - | < 0.001 | - | <0.001 |
| ≥ 17 | 1.56 (1.24 - 1.97) | 1.68 (1.30 - 2.16) |
| Albumin  g/L | < 36 | - | < 0.001 | - | 0.025 |
| ≥ 36 | 0.60 (0.47 - 0.76) | 0.74 (0.56 - 0.96) |
| AFP  ng/ml | <400 | - | 0.001 | - | 0.008 |
| ≥400 | 1.51 (1.19 - 1.93) | 1.41 (1.09 - 1.82) |
| Sex | Male | - | 0.726 |  |  |
| Female | 1.06 (0.78 - 1.44) |  |  |
| Extra-hepatic disease | No | - | 0.521 |  |  |
| Yes | 1.07 (0.86 - 1.34) |  |  |
| Vascular invasion | No | - | 0.013 |  |  |
| Yes | 1.44 (1.08 - 1.91) |  |  |
| Hepatitis B | No | - | 0.792 |  |  |
| Yes | 0.96 (0.69 - 1.33) |  |  |
| Hepatitis C | No | - | 0.070 |  |  |
| Yes | 1.30 (0.98 - 1.73) |  |  |
| Alcohol | No | - | 0.477 |  |  |
| Yes | 1.10 (0.85 - 1.41) |  |  |
| Child Pugh | A | - | 0.003 |  |  |
| B | 1.53 (1.16 – 2.03) |  |  |
| ALBI grade | 1 | - | <0.001 |  |  |
| 2 | 1.92 (1.51 – 2.44) |  |  |
| BCLC | 2 | - | 0.006 |  |  |
| 3 | 1.45 (1.11 – 1.89) |  |  |

Abbreviations: ECOG PS – Eastern Cooperative Group Performance Status; AFP: alpha fetoprotein; ALBI: albumin-bilirubin score; BCLC: Barcelona Clinic Liver Classification

\*Vascular invasion omitted from multivariable model due to missing data. Child Pugh, ALBI and BCLC omitted from multivariable model due to co-linearity with albumin, bilirubin or performance status.

Table 4: First-line systemic therapy trials for HCC in which the TT patients were enrolled.

|  |  |
| --- | --- |
| **Trial name** | **Description** |
| SEARCH(25)  N=41 | Phase III  sorafenib+ erlotinib vs sorafeninb +placebo |
| Nintedanib N=35 | Phase I Nintedanib  Phase II Nintedanib vs Sorafenib |
| BRISK FL(14)  N=26 | Phase III  sorafenib vs brivanib |
| SHARP(3)  N=6 | Phase III RCT  Sorafenib vs placebo |
| E7050  N=3 | Randomised Phase Ib/II  sorafenib +E7050 vs sorafenib |

Reference List

(1) Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015 Mar 1;136(5):E359-E386.

(2) Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015 Mar 14;385(9972):977-1010.

(3) Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008 Jul 24;359(4):378-390.

(4) Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009 Jan;10(1):25-34.

(5) European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012 Apr;56(4):908-943.

(6) Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015 Feb 20;33(6):550-558.

(7) Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19(3):329-338.

(8) Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015 Feb 20;33(6):550-558.

(9) Silverman SL. From randomized controlled trials to observational studies. Am J Med 2009 Feb;122(2):114-120.

(10) Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 2015 Mar 5.

(11) Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012 Oct;57(4):821-829.

(12) Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013 Nov 10;31(32):4067-4075.

(13) Cainap C, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, et al. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2015 Jan 10;33(2):172-179.

(14) Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013 Oct 1;31(28):3517-3524.

(15) Zhu AX, Rosmorduc O, Evans TR, Ross PJ, Santoro A, Carrilho FJ, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2015 Feb 20;33(6):559-566.

(16) Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology 2011 Dec;54(6):2055-2063.

(17) Pinter M, Sieghart W, Hucke F, Graziadei I, Vogel W, Maieron A, et al. Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. Aliment Pharmacol Ther 2011 Oct;34(8):949-959.

(18) Lencioni R, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, et al. First interim analysis of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafeNib) non-interventional study. Int J Clin Pract 2012 Jul;66(7):675-683.

(19) Worns MA, Weinmann A, Pfingst K, Schulte-Sasse C, Messow CM, Schulze-Bergkamen H, et al. Safety and efficacy of sorafenib in patients with advanced hepatocellular carcinoma in consideration of concomitant stage of liver cirrhosis. J Clin Gastroenterol 2009 May;43(5):489-495.

(20) Pressiani T, Boni C, Rimassa L, Labianca R, Fagiuoli S, Salvagni S, et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol 2013 Feb;24(2):406-411.

(21) Ozenne V, Paradis V, Pernot S, Castelnau C, Vullierme MP, Bouattour M, et al. Tolerance and outcome of patients with unresectable hepatocellular carcinoma treated with sorafenib. Eur J Gastroenterol Hepatol 2010 Sep;22(9):1106-1110.

(22) Hollebecque A, Cattan S, Romano O, Sergent G, Mourad A, Louvet A, et al. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. Aliment Pharmacol Ther 2011 Nov;34(10):1193-1201.

(23) Pinter M, Sieghart W, Graziadei I, Vogel W, Maieron A, Konigsberg R, et al. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. Oncologist 2009 Jan;14(1):70-76.

(24) Palmer DH, Hussain SA, Smith AJ, Hargreaves S, Ma YT, Hull D, et al. Sorafenib for advanced hepatocellular carcinoma (HCC): impact of rationing in the United KingdomBr J Cancer 2013 Aug 20;109(4):888-890.

(25) Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013 Oct 1;31(28):3517-3524.