Safety and efficacy of tigatuzumab plus sorafenib as first-line therapy in subjects with advanced hepatocellular carcinoma: A phase 2 randomized study

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Background & Aims: Tigatuzumab is a humanized monoclonal antibody that acts as a death receptor-5 agonist and exerts tumour necrosis factor-related apoptosis-inducing ligand-like activity. In this phase II study, safety and tolerability of the combination of tigatuzumab and sorafenib was evaluated in patients with advanced hepatocellular carcinoma.

Methods: Adults with advanced hepatocellular carcinoma, measurable disease, and an Eastern Cooperative Oncology Group performance score ≤ 1 were enrolled. Eligible subjects were randomly assigned 1:1:1 to tigatuzumab (6 mg/kg loading, 2 mg/kg/week maintenance) plus sorafenib 400 mg twice daily; tigatuzumab 6/6 mg/kg combination group (6 mg/kg loading, 6 mg/kg/week maintenance) plus sorafenib 400 mg twice daily; or sorafenib alone in adults with advanced hepatocellular carcinoma did not meet its primary efficacy end point, although tigatuzumab plus sorafenib is well tolerated in hepatocellular carcinoma.

Keywords: Advanced hepatocellular carcinoma; Combination therapy; CS-1008; Monoclonal antibody; Sorafenib; Tigatuzumab.

Received 8 July 2014; received in revised form 21 April 2015; accepted 2 June 2015; available online 10 June 2015

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Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; RT, radiotherapy; SHARP, a phase III study of Sorafenib in patients with advanced HCC; DR5, death receptor 5; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; BID, twice daily; ECOG, Eastern Cooperative Oncology Group; ICH, International Conference On Harmonisation; GCP, Good Clinical Practice; TTP, time to progression; ORR, objective response rate; OS, overall survival; AEs, adverse events; PD, disease progression; CI, confidence interval; NCI CTC AE, National Cancer Institute’s Common Terminology Criteria for Adverse Events; SAF, serious AE; AFD, alpha-fetoprotein; TIG, Tigatuzumab; SOR, Sorafenib; HR, hazard ratio; SD, standard deviation; TEAE, treatment–emergent AE; PPE, palmar–plantar erythrodysesthesia; AST, aspartate aminotransferase; HAHA, human antihuman antibody; BRISK-PS, Brivanib study in HCC patients at risk post Sorafenib.

Introduction

Hepatocellular carcinoma (HCC) remains one of the most common malignancies worldwide and is a major global cause of cancer-related deaths [1]. Studies have shown that although the incidence of HCC has plateaued or is declining in Asian countries such as China and Japan [2,3], countries such as USA are...
experiencing an acceleration of cases [3,4]. The risk factors for these HCC cases include infection with hepatitis B or C virus (HBV, HCV), non-alcoholic fatty liver disease, and alcoholic liver disease [5].

Common therapies for HCC are resection, transcatheter arterial chemoembolization, radioembolization, partial hepatectomy, cryoablation, percutaneous alcohol injection, microwave therapy, stereotactic body radiotherapy, or external body radiotherapy. Systemic chemotherapy and radiotherapy (RT) have no clear survival benefit and excessive toxicity [6–8]. Patients with advanced-stage disease have unsatisfactory long-term survival outcomes, often owing to underlying liver disease, with high rates of tumour recurrence [9]. There is thus a substantial need for novel treatments for advanced disease.

Sorafenib is a multi-kinase inhibitor with antiangiogenic, pro-apoptotic, and Raf kinase inhibitory activity [10]. Sorafenib showed a survival benefit over placebo in the SHARP (A phase III Study of Sorafenib in Patients with Advanced HCC) and the Asian-Pacific pivotal studies in patients with advanced HCC [11,12], and is now the standard of care for this indication.

Tigatuzumab is a humanized monoclonal antibody that acts as a death receptor 5 (DR5) agonist, exerting tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)-like activity [13]. In a phase I, single agent study in 17 patients with metastatic solid tumours or lymphomas, tigatuzumab showed evidence of preliminary anticancer effects, including 26 months of stable disease in a patient with advanced HCC, and a favourable toxicity profile [14].

In preclinical studies, sorafenib overcame TRAIL resistance in HCC cells and enhances tigatuzumab-induced apoptosis [15]. Several reports have shown the cytotoxic synergy of sorafenib in combination with TRAIL receptor antibodies in various types of cancer cells [16–19]. According to these reports, sorafenib may downregulate Mcl-1, a key molecule playing a critical role in the resistance to TRAIL-induced apoptosis. Thus, administration of tigatuzumab in combination with sorafenib may have synergistic effects for treating HCC. This phase II study aimed to assess the safety and efficacy of tigatuzumab in combination with sorafenib in adult subjects with advanced HCC from Asia and USA.

Patients and methods

Study design

This was a phase II, multi-centre, open-label, randomized study, conducted at 28 study sites in Japan, South Korea, Taiwan, and the USA. All therapies were administered on an outpatient basis, with each treatment cycle lasting three weeks (21 days). As the clinical safety of the proposed weekly regimen of tigatuzumab with daily sorafenib was not established, this trial started with safety cohorts receiving sequentially escalating maintenance doses of tigatuzumab, to gradually reach steady-state levels with repeated dosing, plus regular doses of sorafenib. The loading dose of tigatuzumab 6 mg/kg and the weekly tigatuzumab dosing schedule were largely based on data derived from the phase I dose-escalation study [14].

The dosing schedule for the three safety cohorts is shown in Fig. 1A. Dose-limiting toxicity (DLT) in three subjects in a cohort would halt dose progression, and the prior dose level would be designated the maximum tolerated dose (MTD) (Fig. 1A). If 6 mg/kg/week tigatuzumab was determined not to be above the MTD, the randomized portion of the study would be initiated as planned.

In the randomized portion of the study, 150 eligible subjects were randomly assigned 1:1:1 to: i) tigatuzumab (6 mg/kg loading [or MTD as determined], 2 mg/kg/week maintenance) plus sorafenib 400 mg twice daily (BID); ii) tigatuzumab (6 mg/kg loading [or MTD as determined], 6 mg/kg/week [or MTD] maintenance) plus sorafenib 400 mg BID; or iii) sorafenib 400 mg BID. Tigatuzumab did not reach an MTD in its single agent phase I study, and the tigatuzumab low dosage was based on a population PK model derived from data from this phase I study [14]. The low dose level was predicted to produce serum trough levels in excess of the levels corresponding to maximal efficacy in preclinical xenograft models (data not shown). To assess dose dependency of the efficacy in patients in a phase II study, the higher dose level, previously shown to be safe in phase I, was added in case a higher dose level was required clinically to uniformly penetrate the intra-tumoural space. Human tumours are larger and have higher interstitial pressure than murine tumours, which may impede the uniform biodistribution of antibodies [20]. In some instances, higher doses may provide a sufficient concentration gradient to allow more uniform penetration of tumours, potentially providing more complete target coverage and tumour cell death [21].

Disease assessments were performed at screening/baseline and at the end of every two treatment cycles (six weeks) (Fig. 1B). There was no limit to the number of treatment cycles that could be administered.

Tigatuzumab was administered intravenously over 30 ± 10 min before a dose of sorafenib on day one of each week. Sorafenib was to be taken ≤ 1 h before or ≥ 2 h after meals.

An interactive web response system was used to enrol/randomize subjects. Subjects were provided with a subject identification number when they were enrolled/randomized, and were randomized to one of three treatments according to a randomization schedule. This schedule was computer generated before the randomized portion of the study began by the clinical research organization (ICON Clinical Research, North Wales, PA, USA), under the direction of the sponsor’s biostatistics department. Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1); extrahepatic metastasis and/or macrovessel invasion (yes vs. no), and region (USA, Japan, and Asia [Taiwan and South Korea]). The time between randomization and initiation of treatment was to be ≤ 7 days.

The study was conducted in compliance with the protocol, the ethical principles set forth in the Declaration of Helsinki, International Conference on Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP), and applicable regulatory requirement(s).

Participants

The key inclusion criteria were: subjects aged ≥ 18 years; histologically or cytologically confirmed HCC or clinical diagnosis of HCC; advanced disease; measurable disease based on RECIST criteria (version 1.1) [22] of ≥ 1 untreated target lesion that can be measured in one dimension; ECOG performance status 0 or 1; Child–Pugh class A; life expectancy of ≥ 12 weeks; and adequate organ and bone marrow function.

Key exclusion criteria included: any prior systemic therapy for HCC; RT, major surgical procedure, or use of any investigational agent within four weeks and minor surgical procedures within two weeks of the first dose of study treatment; anticipation of need for RT or a major surgical procedure during the study; history of organ transplantation; or clinically significant, severe, active infection requiring intravenous antibiotics.

Outcomes

The primary endpoint was time to progression (TTP). Secondary endpoints were objective response rate (ORR), overall survival (OS), and safety (adverse events [AEs] and clinical laboratory evaluations).

Assessments

Efficacy assessments were based on tumour measurements obtained from serial radiographs and clinical measurements (e.g., CT scans) performed at baseline then after the end of every two treatment cycles, and survival status. Tumour measurements, disease progression (PD), ORR, and variables based on response to treatment were assessed in accordance with RECIST (version 1.1) [22]. An independent radiological review of tumour measurements and independent review of response rates was also carried out at Columbia University, NY, USA.

TTP was defined as the time from the date of registration/randomization until PD according to RECIST criteria (version 1.1) [22] or symptomatic progression (defined as deterioration to ECOG performance status 4).

All clinical AEs occurring ≤ 30 days after the last dose of study medication were recorded. After discontinuation from study treatment, subjects were to be contacted every three months, until death or for up to 16 months after last subject randomization, to obtain information concerning subsequent treatments and survival status.

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The primary efficacy analysis was performed on the full analysis set, which comprised all subjects in the randomized portion of the study who received \( P_1 \) dose of study drug. The safety analysis set comprised all subjects, in both the safety cohort and randomized portion, who received any amount of study drug (tigatuzumab or sorafenib) and had \( P_1 \) safety assessment.

For sample size planning in the randomized portion, based on the primary endpoint of TTP, 150 subjects randomized with a 1:1:1 ratio to one of the three treatment groups was considered to provide reasonable precision for the estimation of the hazard ratio (HR) between treatment groups.

A Cox proportional hazards model was employed to estimate the HR (and 95% confidence interval [CI]) between treatment groups. The model included, as factors, treatment groups and stratification factors used in randomization (Fig. 1B). Other important pre-specified prognostic variables such as age and HBV/HCV infection status were also explored and included in the model as appropriate. In addition, a stratified log-rank test was employed to assess whether there was a difference between sorafenib treatment alone and sorafenib in combination with tigatuzumab 6/2 or 6/6 mg/kg per week (both separately and combined), with \( p \) values presented for the comparisons. Kaplan–Meier product limit estimates for TTP and OS were calculated and plotted for each treatment group, and the estimate of median TTP and OS provided, along with the 95% CI.

AEs were coded using the Medical Dictionary for Regulatory Activities and assigned grades based on National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. There was no formal safety and data monitoring board. Toxicity was assessed by the sponsor/ICON medical monitor and investigator.

Results

The first subject enrolled in the study on 9 July 2010 and the last subject completed on 9 September 2013.

Safety cohort

Nine subjects were enrolled in the safety cohort (\( n = 3 \) per tigatuzumab 2, 4, or 6 mg/kg weekly maintenance dosing group). Median (range) age was 49 (37–81) years, six (66.7%) subjects were men, and all nine were Asian. Two-thirds (66.7%) of subjects had an ECOG performance status of 0. All had received prior cancer therapy. As of the primary analysis cut-off date (13 July 2012), all nine subjects discontinued from the study: 7 (77.8%) due to PD, 1 (11.1%) due to a serious AE (SAE) or AE, and 1 (11.1%) due to withdrawal of consent.

No DLTs were observed in the safety cohort and the MTD of tigatuzumab was not reached. Therefore, the randomized portion of the study was conducted using the tigatuzumab loading dose of 6 mg/kg.

Randomized portion

Patients

In total, 163 subjects were randomized to treatment (Fig. 2). The median (range) age was 63 (27–84) years, 134 (82.7%) subjects were men and the majority (159 [98.1%]) were Asian. Baseline demographics and clinical characteristics for randomized
subjects are summarized in Table 1. Baseline alpha-fetoprotein (AFP) was not well balanced, with low AFP favouring the tigatuzumab high-dose arm. As this was a randomized trial with no stratification of baseline AFP, this observation is a random effect, as no evidence of other factors are noted for this imbalance.

Within the efficacy analysis set, the number of subjects with normal AFP $\leq 200$ IU/ml in sorafenib (SOR) alone, tigatuzumab (TIG) 6/2 mg/kg + SOR, and TIG 6/6 mg/kg + SOR groups is 23 (41.8%), 19 (35.8%), and 25 (46.3%), respectively; the number of subjects with baseline AFP $>200$ IU/ml is 32 (58.2%), 34 (64.2%), and 28 (51.9%), respectively; and the number of subjects with baseline AFP $>400$ IU/ml is 31 (56.4%), 32 (60.4%), and 23 (42.6%) respectively. As of the primary analysis cut-off date, 11 of the 163 randomized subjects remained in the study and 152 had discontinued, mostly due to PD (Fig. 2). In total, 162 were included in the full analysis set, which included the originally assigned groups. All subjects had discontinued from the study as of 9 September 2013.

### Efficacy

HRs for comparisons of TTP were 1.12 (95% CI 0.69–1.80) for TIG 6/2 mg/kg + SOR vs. SOR alone ($p=0.657$), and 1.15 (95% CI 0.73–1.81) for TIG 6/6 mg/kg + SOR vs. SOR alone ($p=0.548$). Median (95% CI) TTP was 3.0 (2.6–5.5) months in the TIG 6/2 mg/kg + SOR group, 3.9 (2.7–5.3) months in the TIG 6/6 mg/kg + SOR group, and 2.8 (1.5–6.6) months in the SOR alone group. Neither of the treatment differences for the comparison with SOR alone were statistically significant (Fig. 3A). The combined $p$ value for both TIG + SOR groups vs. SOR alone was 0.794.

TTP as assessed by independent radiological review showed similar results, especially in the higher dose TIG and SOR alone groups: median TTP (95% CI) of 4.0 (2.8–5.4) months with TIG 6/2 mg/kg + SOR ($p=0.898$ vs. SOR alone), 4.1 (2.7–5.7) months with TIG 6/6 mg/kg + SOR ($p=0.868$ vs. SOR alone), and 2.8 (1.6–5.6) months with SOR alone. The combined $p$ value for both TIG + SOR groups vs. SOR alone was 0.790.

### Table 1. Patient baseline demographics and clinical characteristics (full analysis set).

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<th>Tigatuzumab 6/6 mg/kg + sorafenib (n = 54)</th>
<th>Sorafenib (n = 55)</th>
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<td>53 (98.1)</td>
<td>54 (98.2)</td>
<td>159 (98.1)</td>
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<td>11 (20.0)</td>
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<td>Radiation therapy, n (%)</td>
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<td>34 (63.0)</td>
<td>36 (65.5)</td>
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<td>Cancer surgery, n (%)</td>
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<td>9 (16.7)</td>
<td>7 (12.7)</td>
<td>25 (15.4)</td>
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<td>Locoregional therapy, n (%)</td>
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<td>25 (46.3)</td>
<td>26 (47.3)</td>
<td>75 (46.3)</td>
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<tr>
<td>Median AFP, IU/ml (range)</td>
<td>33 (62.3)</td>
<td>32 (59.3)</td>
<td>30 (54.5)</td>
<td>95 (58.6)</td>
<td></td>
</tr>
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</table>

AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus.

*6 mg/kg loading dose followed by 2 mg/kg maintenance dose.

*6 mg/kg loading dose followed by 6 mg/kg maintenance dose.

*Cytostatics, chemotherapeutics, biologics and small molecules.
**Fig. 3.** Efficacy outcomes (full analysis set): (A) Time to tumour progression and (B) overall survival at the OS update. Censored observations indicated by a circle, triangle, or square. TIG, Tigatuzumab; SOR, Sorafenib.
We examined the effect of hepatitis viral infection status on the efficacy results. The median TTP in patients with HCV in the SOR alone, TIG 6/2 mg/kg + SOR, and TIG 6/6 mg/kg + SOR groups was 4.2 months, 3.0 months, and 6.0 months, respectively; and in patients with HBV, 2.6 months, 4.0 months, and 2.7 months, respectively. The median OS in patients with HCV in the SOR alone, TIG 6/2 mg/kg + SOR, and TIG 6/6 mg/kg + SOR groups and HCV groups was 9.2 months, 7.6 months, and 13.9 months, respectively; and in patients with HBV, 6.2 months, 9.3 months, and 9.0 months, respectively.

The effect of country of origin on efficacy was also evaluated. The median TTP in patients in Taiwan in the SOR alone, TIG 6/2 mg/kg + SOR, and TIG 6/6 mg/kg + SOR groups was 2.3 months, 5.4 months, and 2.7 months, respectively; in South Korea, 2.0 months, 5.5 months, and 2.8 months, respectively; and in Japan, 8.3 months, 2.9 months, and 7.2 months, respectively. The median OS in patients in Taiwan in the SOR alone, TIG 6/2 mg/kg + SOR, and TIG 6/6 mg/kg + SOR groups was 4.9 months, 9.4 months, and 11.1 months, respectively; in South Korea, 7.6 months, 9.3 months, and 9.7 months, respectively; and in Japan, 7.6 months, and 15.0 months, respectively. Three patients were enrolled from the United States, insufficient data for a separate evaluation of efficacy in that region.

The sample sizes and numbers of events in each of these subgroups are small to moderate, and the associated confidence intervals of median PFS/OS are wide and overlapping between treatment groups. Additionally, Cox regression model analysis does not suggest an interaction between the treatment groups and any of the following factors: HBV infection status, HCV infection status, and region.

At study end, the number of subjects with radiographic progression or symptomatic progression was 34 (64.2%), 41 (75.9%), and 37 (67.3%) in the TIG 6/2 mg/kg + SOR, TIG 6/6 mg/kg + SOR, and SOR alone groups, respectively. These proportions were notably lower in all treatment groups following independent radiological review: 54.7%, 53.7%, and 58.2%.

At the final OS update, median (95% CI) OS was highest in the group receiving TIG 6/6 mg/kg + SOR (12.2 [9.0–15.0] months). In comparison, median OS was 8.2 months in the TIG 6/2 mg/kg + SOR (95% CI, 5.7–10.4) and the SOR alone groups (95% CI, 4.9–13.4). Neither of the treatment differences for the comparison with SOR alone were statistically significant (Fig. 3B). The combined p value for both TIG + SOR groups vs. SOR alone was 0.737.

No subjects achieved a complete response. A partial response was confirmed in 5.7% of subjects in the TIG 6/2 mg/kg + SOR group, 14.8% in the TIG 6/6 mg/kg + SOR group, and 10.9% in the SOR alone group. In subjects with a partial response, the mean (SD) duration of response was 27.8 (13.5) weeks for subjects in the TIG 6/2 mg/kg + SOR group (n = 3), 14.0 (10.6) weeks for those in the TIG 6/6 mg/kg + SOR group (n = 8), and 31.4 (18.8) weeks in the SOR alone group (n = 6). Stable disease was observed in 49.1% of subjects receiving TIG 6/2 mg/kg + SOR, 53.7% receiving TIG 6/6 mg/kg + SOR, and 43.6% receiving SOR alone. In subjects with stable disease, the mean (SD) duration of response was 21.6 (13.0) weeks with TIG 6/2 mg/kg + SOR treatment (n = 26), 24.5 (16.6) weeks with TIG 6/6 mg/kg + SOR (n = 29), and 23.3 (14.6) weeks with SOR alone (n = 24). Response rates as assessed by independent review showed similar results (data not shown).

Pre-specified subgroup analyses performed to identify characteristics potentially predictive of a longer TTP following study treatment showed that there were no significant interactions between treatment and any of the subgroup classification factors (Fig. 4).

Exploratory

An exploratory analysis was performed with the Cox proportional hazards model of OS incorporating baseline AFP level, as this was imbalanced at baseline. At the final OS update, the HR (95% CI) for the comparison between TIG 6/2 mg/kg + SOR and SOR treatment alone was 1.24 (0.77–1.99) (p = 0.372), and 0.84 (0.52–1.35) for the comparison between TIG 6/6 mg/kg + SOR and SOR treatment alone (p = 0.466). After incorporating logarithm of baseline AFP level as a covariate in the exploratory analysis, the HR (95% CI) estimates were 1.27 (0.79–2.05) and 0.93 (0.58–1.50), respectively (p = 0.321 and 0.760, respectively).

Safety (includes safety cohort)

In total, 171 (99.4%) subjects were included in the safety analysis set, which included the originally assigned groups. Mean duration of treatment ranged from 15.6 to 19.1 weeks for tigatuzumab, and 15.4 to 18.9 weeks for sorafenib across all treatment groups. Mean (SD) dose intensity of tigatuzumab was 3.96 (1.70) mg/kg/week.

Safety data are based on the primary analysis. Most subjects experienced ≥1 treatment-emergent AE (TEAE) assessed as Grade 3 or higher (Supplementary Table 1). In total, 75.9% (88/116) of tigatuzumab-treated subjects experienced ≥1 TEAE that was considered related to tigatuzumab, and 98.3% of the safety cohort experienced ≥1 treatment-emergent AE in the treatment groups.

Table 3. Sensitivity analysis: Hazard ratio and p-value for interaction between treatment and subgroup classification factor

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard ratio (95% CI)</th>
<th>p value† for interaction between treatment and subgroup class</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV infection status</td>
<td>1.685 (0.876–3.242)</td>
<td>0.110</td>
</tr>
<tr>
<td>HBV infection status (yes vs. no)</td>
<td>1.195 (0.671–2.128)</td>
<td></td>
</tr>
<tr>
<td>Region (Taiwan vs. Japan)</td>
<td>2.387 (0.951–5.993)</td>
<td>0.057</td>
</tr>
<tr>
<td>Region (South Korea vs. Japan)</td>
<td>1.460 (1.392–8.599)</td>
<td></td>
</tr>
<tr>
<td>Region (TIG vs. SOR)</td>
<td>2.091 (0.898–4.865)</td>
<td></td>
</tr>
<tr>
<td>Baseline ECOG (T1 vs. 0)</td>
<td>2.478 (1.266–4.849)</td>
<td>0.091</td>
</tr>
<tr>
<td>Baseline ECOG (TIG vs. SOR)</td>
<td>1.633 (0.923–2.891)</td>
<td></td>
</tr>
<tr>
<td>Extrahepatic metastasis* (yes vs. no)</td>
<td>0.909 (0.427–1.938)</td>
<td>0.651</td>
</tr>
<tr>
<td>Extrahepatic metastasis* (TIG vs. SOR)</td>
<td>0.919 (0.401–2.104)</td>
<td></td>
</tr>
<tr>
<td>HCV infection status</td>
<td>1.757 (0.371–8.542)</td>
<td></td>
</tr>
<tr>
<td>HCV infection status (yes vs. no)</td>
<td>1.211 (0.743–2.281)</td>
<td>0.062</td>
</tr>
<tr>
<td>HCV infection status (TIG vs. SOR)</td>
<td>1.416 (0.774–2.593)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4. Cox proportional hazards model analysis of time to tumour progression, including interaction between treatment and subgroup classification factor (full analysis set). ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; SOR, sorafenib; TIG, tigatuzumab.

*Includes microvessel invasion. †Wald test.
experienced >1 TEAE that was considered related to sorafenib. The most common tigatuzumab-related TEAE was decreased appetite (27.6% of all tigatuzumab-treated subjects), and the most common sorafenib-related TEAE was diarrhoea (40.0–66.7% of subjects across all treatment groups).

Among all tigatuzumab-treated subjects, the most common TEAEs were palmar-plantar erythrodysesthesia (PPE) syndrome, diarrhoea, decreased appetite, increased aspartate aminotransferase (AST), and alopecia (Table 2), and the most common Grade 3–5 TEAEs were increased AST, increased lipase, hypophosphatemia, PPE syndrome and hypertension (Supplementary Table 1). During the randomized portion of the study, Grade 3–5 TEAEs (most commonly disease progression) occurred with similar frequency across all three treatment groups (Supplementary Table 1). In total, 12.1% and 14.7% discontinued tigatuzumab or sorafenib, respectively, due to TEAEs. Discontinuation of sorafenib due to TEAEs ranged from 11.1% to 32.7% across all treatment groups. The percentage of subjects with TEAEs leading to death ranged from 10.9% to 20.0% across all treatment groups; none of these TEAEs were considered related to tigatuzumab. The percentage of subjects who died during the study or follow-up ranged from 44.4% (safety cohort) to 61.8% (randomized to sorafenib alone).

The most common treatment-emergent SAEs were ascites in tigatuzumab-treated subjects (n = 5), and hepatic encephalopathy in sorafenib-treated subjects (n = 4).

No clinically meaningful mean changes from baseline in hematology, serum chemistry, or coagulation values were
analyses were not performed, as is becoming increasingly impor-

tation and clarification[29]. Finally, HCC biopsy and tissue

in TTP, but not in OS, was observed. Thus, appropriate end-

at Risk Post sorafenib) of brivanib in advanced HCC, where a ben-

recent phase III BRISK-PS study (Brivanib Study in HCC Patients

studies assessing primary treatments for HCC, as recommended

throughout the Kaplan–Meier curves, as reflected in the OS

groups, and this apparent advantage in OS is not maintained

centrations were sufficient to mediate clinical effects. However,

suggested that the proportion of subjects with radiographic or

lysis review yielded similar results for TTP, although the data

which favoured the high-dose tigatuzumab group, giving the ini-

 Serum tigatuzumab concentrations increased dose-dependently, and

for both dose groups exceeded the target concentration derived

from preclinical data (data on file), suggesting that the drug con-

centrations were sufficient to mediate clinical effects. However,

there were imbalances in AFP at baseline between the treatment

groups, and this apparent advantage in OS is not maintained

in baseline AFP, a prognostic marker for HCC[27]

ient with results from prior phase II studies of tigatuzumab in

Although allergic and anaphylactic reactions may occur with

therapeutic proteins [25], there were no reports of anaphylactic

reactions or severe hypersensitivity in this study, and there was

no evidence of the HAHA antibody. These safety data are consis-

tent with results from prior phase II studies of tigatuzumab in

combination with other anticancer therapies, such as gemc-

avitin and carboplatin/paclitaxel [14,26].

This study has a few limitations. There was a large imbalance

between groups in baseline AFP, a prognostic marker for HCC [27]

which favoured the high-dose tigatuzumab group, giving the ini-

tial impression of a larger advantage in OS at the median. Serum

tigatuzumab concentrations increased dose-dependently, and

for both dose groups exceeded the target concentration derived

from preclinical data (data on file), suggesting that the drug con-

centrations were sufficient to mediate clinical effects. However,

there were imbalances in AFP at baseline between the treatment

groups, and this apparent advantage in OS is not maintained

throughout the Kaplan–Meier curves, as reflected in the OS

HRs, which are near one; further, adjustment for the imbalance

in AFP brings the HR even closer to one. In addition, the use of

TTP (as a surrogate of OS) as the standard primary end point in

studies assessing primary treatments for HCC, as recommended

by the American Association for the Study of Liver Diseases

[28], is currently under question, following results from the

recent phase III BRISK-PS study (Brivanib Study in HCC Patients

at Risk Post sorafenib) of brivanib in advanced HCC, where a ben-

efit in TTP, but not in OS, was observed. Thus, appropriate end-

points for HCC primary treatment studies require further

investigation and clarification [29]. Finally, HCC biopsy and tissue

analyses were not performed, as is becoming increasingly impor-

tant in HCC clinical trials.

Discussion

With limited therapeutic options available for advanced HCC, novel treatments are warranted to improve prognoses. This phase II randomized study was conducted to assess the safety and effi-
cacy of the novel humanized monoclonal antibody tigatuzumab in combination with the standard of care, sorafenib, in adults

with advanced HCC from Japan, South Korea, Taiwan, and USA.

In the safety cohort portion of the study, there were no observed DLTs for tigatuzumab, up to a dose of 6 mg/kg weekly,

and the MTD for the drug was not reached. In the randomized portion of the study, no significant differences between the treat-

ment groups were observed for the primary efficacy endpoint, TTP, or the secondary efficacy endpoints. The independent radi-

ological review yielded similar results for TTP, although the data

suggested that the proportion of subjects with radiographic or

symptomatic progression at study end was notably lower across
treatment groups. This is likely due to differences in reviewer
judgment.

Generally, the combination of tigatuzumab and sorafenib pro-

vided acceptable tolerability in adults with advanced HCC. The

most common TEAEs (e.g. PPE syndrome, diarrhoea, decreased

appetite) were consistent with sorafenib use [23] or underlying

liver disease [24]. Reassuringly, no TEAEs leading to death were

considered by the investigator to be related to tigatuzumab.

Although allergic and anaphylactic reactions may occur with

therapeutic proteins [25], there were no reports of anaphylactic

reactions or severe hypersensitivity in this study, and there was

no evidence of the HAHA antibody. These safety data are consist-

ent with results from prior phase II studies of tigatuzumab in

combination with other anticancer therapies, such as gemc-

avitin and carboplatin/paclitaxel [14,26].

This study has a few limitations. There was a large imbalance

between groups in baseline AFP, a prognostic marker for HCC [27]

which favoured the high-dose tigatuzumab group, giving the ini-

tial impression of a larger advantage in OS at the median. Serum

tigatuzumab concentrations increased dose-dependently, and

for both dose groups exceeded the target concentration derived

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points for HCC primary treatment studies require further

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analyses were not performed, as is becoming increasingly impor-

tant in HCC clinical trials.

Conclusions

Tigatuzumab in combination with sorafenib vs. sorafenib alone in

adults with advanced HCC did not meet its primary efficacy end-

point, although the combination is well tolerated.

Conflict of interest

A-L.C was a consultant for Daiichi Sankyo, Inc.; Merck Serono;
Eisai; Jennerex and Exelixis and received research funding from
Sanofi-Aventis; Chugai and MSD. Y-K.K has received research
grants from Bayer and worked as an advisory board member
for Bayer. T.A. is an employee of Novartis Pharmaceuticals
Corporation and is an ex-employee of Daiichi Sankyo, Inc. Q.W.

is an employee of Daiichi Sankyo, Inc. J.G. is an employee
of Daichi Sankyo, Inc. and owns stock in the company. S.S. is an
employee of Daichi Sankyo, Co., Ltd. R.A.B. is a stockholder
in Johnson & Johnson, Inc. and in Daiichi Sankyo Pharma
Development (DSPD) and was a full time employee of DSPD at
the time of the study.

The remaining authors declared that they do not have any-
thing to disclose regarding funding or conflict of interest with
respect to this manuscript.

Financial support

This work was supported with funding from Daiichi Sankyo
Pharma Development, a division of Daiichi Sankyo, Inc. Editorial
assistance was provided by Sola Neunie,

MSC, of PAREXEL, and was funded by Daiichi Sankyo Pharma
Development.

Author’s contributions

A-L.C. contributed to the study concept and design, acquisition
of data, analysis and interpretation of data, critical revision of

the manuscript for important intellectual content, and study

supervision.

Y-K.K. contributed to the study concept and design, acquisi-
tion of data, analysis and interpretation of data, and critical revi-
sion of the manuscript for important intellectual content.

A.R.H. contributed to the study concept and design, acquisi-
tion of data, analysis and interpretation of data, and critical revi-
sion of the manuscript for important intellectual content.

H.Y.L. contributed to the study concept and design, acquisi-
tion of data, analysis and interpretation of data, drafting of the

manuscript, and critical revision of the manuscript for important

intellectual content.

B-Y.R. contributed to the study concept and design, acquisi-
tion of data, analysis and interpretation of data, critical revision

of the manuscript for important intellectual content, and study

supervision.

C-H.H. contributed to the analysis and interpretation of data
and critical revision of the manuscript for important intellectual

content.

I-S.S. contributed to the acquisition of data and drafting of the

manuscript.
Research Article

N.I. contributed to the acquisition of data and drafting of the manuscript.

T.A. contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, administrative, technical, or material support, and study supervision.

Q.W. contributed to the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis.

J.G. contributed to the study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision.

S.S. contributed to the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision.

R.A.B. contributed to the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision.

M.K. contributed to the acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision.

ClinicalTrials.gov Identifier: NCT01033240.

Acknowledgements

This work was supported with funding from Daiichi Sankyo Pharma Development, a division of Daiichi Sankyo, Inc. Editorial assistance was provided by Sola Neunie, MSc, of PAREXEL, and was funded by Daiichi Sankyo Pharma Development. The authors thank all the principal investigators who enrolled patients in this trial. The authors also wish to acknowledge Mendel Jansen, BSc, of Daiichi Sankyo Development, for his contribution to the study. The authors also thank Lawrence Schwartz, MD, of Columbia University, New York, NY, for conducting the independent radiological review.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2015.06.001.

References