Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare Pharmaceuticals Inc.	
Study Number:	12918	2008-005056-24 EudraCT No.: 2008-005056-24
Study Phase:	2	
Official Study Title:	A Phase II randomized, double-blind, placebo-controlled study of sorafenib or placebo in combination with transarterial chemoembolization (TACE) performed with DC Bead and doxorubicin for intermediate stage hepatocellular carcinoma (HCC)	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Sorafenib, BAY 43-9006	
Name of Active Ingredient:	Sorafenib	
Dose and Mode of Administration:	400 mg (2 tablets of 200 mg) twice daily (bid) Oral	
Reference Therapy/Placebo		
Reference Therapy:	Placebo	
Dose and Mode of Administration:	2 tablets bid Oral	
Duration of Treatment:	Patients received repeated treatment with TACE plus sorafenib or placebo. TACE continued until the secondary endpoint of untreatable progression was met. In the event of radiological progression confined to the liver, subjects continued the study treatments, i.e., TACE performed with DC Bead plus blinded study drug (sorafenib or placebo), as long as the subjects were benefiting from TACE. Subjects, for whom it was medically appropriate to stop TACE administration, were allowed to continue to receive blinded study drug per protocol until disease progression was documented; subjects who achieved a complete response [CR] should continue receiving blinded study drug, while those subjects who had met certain untreatable progression criteria could continue receiving blinded study drug.	
Studied period:	Date of first subjects' first visit:	30 MAR 2009
	Date of last subjects' last visit:	08 FEB 2013

Study Center(s):	The study was conducted at 84 centers in 13 countries: China (6), South Korea (4), Italy (10), Spain (13), France (10)[1], Germany (12), United States of America (11), Belgium (4), Taiwan (3), Australia (6), Austria (2), Canada (3), Singapore (1). [1] One center in France was not displayed due to missing center name information in the database. All patients enrolled in this center were correctly analyzed in the ITT and Safety population.
Methodology:	Tumor response and disease progression assessments using modified Response Evaluation Criteria in Solid Tumors (RECIST) (v. 1.0) criteria were based on a blinded review of CT/MRI scans of the abdomen and pelvis by an independent centralized radiological assessment and by the Investigator. Non-target lesions and extra-hepatic recurrences were also assessed. Overall survival (OS): All randomized patients were followed for survival information. After discontinuation of study drug treatment, patients continued to the post-treatment follow-up period and were contacted every 3 months until the last OS analysis Radiological assessments were performed at screening, at Cycle 3 and every 2 cycles thereafter (every 8 weeks) during the treatment period. Patient reported outcome (PRO) was evaluated applying FACT-Hep and EQ-5D questionnaires at screening, Day 1 of Cycle 1, and then on the first day of every second cycle during study treatment. An independent Data Monitoring Committee (DMC) was instituted for this study to evaluate the safety and efficacy data during the conduct of the study. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 was used for assessment of toxicity and serious adverse event reporting. Safety analyses were based on the valid for safety (SAF) population, i.e. all patients randomized to treatment who received any study medication.

Indication/ Main Inclusion Criteria:	Intermediate stage HCCMale and female patients of ≥18 years of age with intermediate stage HCC: • Unresectable, multinodular asymptomatic tumor without vascular invasion or extrahepatic spread • Confirmed Diagnosis of HCC: - Cirrhotic patients: Clinical diagnosis by AASLD criteria: o HCC could be defined in cirrhotic subjects by one imaging technique (CT scan, MRI, or second generation contrast ultrasound) showing a nodule larger than 2 cm with contrast uptake in the arterial phase and washout in venous or late phases or two imaging techniques showing this radiological behavior for nodules of 1-2 cm in diameter. o Cytohistological confirmation was required for subjects who did not fulfill these eligibility criteria. - Non-cirrhotic subjects: For subjects without cirrhosis, histological or cytological confirmation was mandatory . - Documentation of original biopsy for diagnosis was acceptable. • Child Pugh class A without ascites • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 • At least one unidimensional lesion measurable according to the RECIST criteria by CT-scan or MRI • Life expectancy of at least 12 weeks • Lesions had previously not been treated with local therapy such as resection of HCC, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) or cryoablation were not to be selected as the target lesions. • No prior transarterial embolization (with or without chemotherapy). Adequate bone marrow, liver and renal function as assessed by clinical laboratory tests.

Study Objectives:	To evaluate the efficacy and safety of TACE (transarterial chemoembolization) performed with DC Bead and doxorubicin plus sorafenib versus TACE performed with DC Bead and doxorubicin plus placebo for the treatment of intermediate stage HCC. **Primary efficacy objective:** To demonstrate the superiority of sorafenib over placebo with regard to time to progression (TTP) in patients with intermediate stage HCC receiving TACE performed with DC Bead. **Secondary objectives:** • Overall Survival (OS) • Time to untreatable progression (TTUP) • Time to vascular invasion / extra-hepatic spread • Safety **Other objectives:** • Patient-Reported Outcome (PRO) as assessed by FACT-Hep and EQ-5D questionnaire • Evaluation of biomarkers • Response Rate (according to RECIST Amendment)

Evaluation Criteria:	**Efficacy** The primary efficacy variable was TTP based on the intent to treatment population (ITT) population and assessed by an independent centralized radiological review. TTP was defined as the time (days) from randomization to radiological confirmed disease progression. Secondary efficacy variables were: • Overall survival, defined as the time from randomization to death due to any cause. • Time to untreatable progression, defined as the time from randomization to untreatable progression, i.e., until the occurrence of events leading to contraindication to therapy according to at least one of the following criteria: o Failure to achieve objective response after at least two TACE sessions in the treated tumor nodule. o Appearance of contraindications to TACE performed with DC Bead according to selection criteria, assessed prior to the TACE procedure being performed at Cycles 3, 7, 13, 19, and where optional TACE procedures were required. o Clinical progression to ECOG Performance Status ≥2. • Time to vascular invasion/extrahepatic spread, defined as the time from randomization to the radiological evidence of vascular invasion/extrahepatic spread confirmed by CT/MRI scan. Other efficacy variables • Response rate (RR), defined as the percentage of patient achieving either a confirmed CR or partial tumor response (PR) according to the RECIST Amendment. • Patient reported outcome (PRO) measured by The Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and the EuroQol-5D (EQ-5D). • Evaluation of biomarkers **Safety:** Safety was assessed based on the results of vital signs, electrocardiogram (ECG) data, weight, laboratory values, adverse events (AE) and serious adverse events (SAEs) reported from signing the informed consent until 30 days of the last dose of study drug. Adverse events/SAEs reported during treatment until 30 days of the last dose of study drug were taken into account as 'treatment-emergent'.

Statistical Methods:	The primary efficacy endpoint was TTP based on the ITT population. The two treatment groups (sorafenib + TACE and placebo + TACE) were compared using a one-sided log-rank test with an overall $\alpha = 0.15$ stratified by the factors region and alpha-fetoprotein level at baseline. The hazard ratio for TTP and 95% confidence interval were provided using stratification factors. Kaplan-Meier estimates and survival curves were presented for each treatment group. All TTP analyses were performed based on an independent central assessment and based on the Investigator's assessment. The TTP analysis based on the Investigator's assessment was considered secondary to the analysis based on an independent assessment. Subgroup analyses of TTP were performed in the ITT population for the following variables: sex, age group, region, prior therapy/therapeutic procedure, etiology of underlying disease, duration of treatment, bilirubin at baseline, Child Pugh at baseline, planned dose received, dose interruption, and best objective response. The secondary efficacy endpoints OS, TTUP, and time to vascular invasion/extrahepatic spread based on the Investigator's assessment and on the ITT population were analyzed as described for the primary efficacy endpoint. Subgroup analyses of OS, TTUP, and time to vascular invasion/extrahepatic spread were performed in the ITT population for the following variables: sex, age group, and region.. Tumor response and disease progression were evaluated based on the Investigator's assessment using RECIST Amendment tumor response criteria. As supportive analysis, analyses were repeated using independently-assessed RECIST tumor response criteria. The safety data were summarized using descriptive statistics for the SAF population, and treatment-emergent AE data were also presented for Asian and non-Asian SAF subpopulations. The final TTP analysis was based on 179 disease progression events, assessed by an independent panel of radiologist and observed up to and including the data cut-off date of 29 JUL 2011. The statistical methods applied for PRO analyses will be reported in a separate addendum to this Clinical Study Report.
Number of Subjects:	Planned: In total 300 patients, 150 patients per treatment group Analyzed: 307 patients randomized (ITT, FAS), 304 treated (SAF)

Analysis set	Placebo + TACE	Sorafenib + TACE	Total
ITT (FAS)	153	154	307
SAF	151	153	304

ITT – Intention-to-treat; FAS – Full analysis set; SAF – safety analysis set.

Study Results

Results Summary — Subject Disposition and Baseline

Out of 450 screened HCC patients, 307 patients were randomized: 154 to the sorafenib + TACE group and 153 to the placebo + TACE group. A patient disposition for the ITT populations is presented in Table Error**! No text of specified style in document.**-1.

Table Error! No text of specified style in document.**-1 Patient disposition (FAS)**

	Placebo + TACE		Sorafenib + TACE		Total	
	n	(%)	n	(%)	n	(%)
Randomized (FAS)	153	(100.0%)	154	(100.0%)	307	(100.0%)
Treated (SAF)	151	(98.7%)	153	(99.4%)	304	(99.0%)
No discontinuation	21	(13.7%)	24	(15.6%)	45	(14.7%)
Discontinuation with unknown reason	0	–	0	–	0	–
Discontinuation	132	(86.3%)	130	(84.4%)	262	(85.3%)
Primary reason						
Adverse event	26	(17.0%)	41	(26.6%)	67	(21.8%)
Investigator decision, not protocol driven	11	(7.2)	17	(11.0%)	28	(9.1%)
Non-compliant with study medication	1	(0.7%)	3	(1.9%)	4	(1.3%)
Progression measurement proven	13	(8.5%)	5	(3.2%)	18	(5.9%)
Consent withdrawn	6	(3.9%)	10	(6.5%)	16	(5.2%)
Second malignancy	1	(0.7%)	0	–	1	(0.3%)
Technical problems	1	(0.7%)	2	(1.3%)	3	(1.0%)
Untreatable disease progression	63	(41.2%)	45	(29.2%)	108	(35.2%)
Patient convenience	0	–	2	(1.3%)	2	(0.7%)
Lost-to follow-up	1	(0.7%)	0	–	1	(0.3%)
Protocol deviation	9	(5.9%)	5	(3.2%)	14	(4.6%)

Abbreviations: ITT – intention-to-treat; FAS – Full analysis set; SAF – Safety analysis set.

Demographic and baseline characteristics are summarized in Table Error**! No text of specified style in document.**-2.

The treatment groups were similar for **demographic and baseline characteristics**. Most patients were men (87.7% versus 82.4% in the sorafenib + TACE and placebo + TACE groups), and approximately half of the patients in both treatment groups were <65 years old (50.0% versus 53.6%), White (59.6% versus 62.1%), and had an alpha-fetoprotein level at baseline of <400 ng/mL (73.4% versus 73.2%).

Most patients showed more than one and up to 5 target lesions in the investigator's assessment, with 2 target lesions being most frequent in 37.7% of patients in the sorafenib +TACE group and in 32.0% of patients in the placebo + TACE group. The further frequencies for target lesions per patients were 21.4% versus 21.6% for 3 lesions, 7.8% versus 11.8% for 4 lesions, and 13.6% versus 14.4% for 5 lesions. Zero non-target lesions were seen in 46.8% of patients in the sorafenib + TACE group and in 47.7% of patients in the placebo + TACE group.

Table Error! No text of specified style in document.**-2 Baseline demographic characteristics (FAS)**

Characteristic	Placebo + TACE (N = 153)		Sorafenib + TACE (N = 154)		Total (N = 307)	
	n	(%)	n	(%)	n	(%)
Sex						
Male	126	(82.4%)	135	(87.7%)	261	(85.0%)
Female	27	(17.6%)	19	(12.3%)	46	(15.0%)
Age (years) at enrollment						
Mean	62.7		62.5		62.6	
Median (range)	63.0 (24 – 87)		64.5 (22 – 82)		64.0 (22 – 87)	

Age group (years)						
<65	82	(53.6%)	77	(50.0%)	159	(51.8%)
65 – 74	48	(31.4%)	52	(33.8%)	100	(32.6%)
≥75	23	(15.0%)	25	(16.2%)	48	(15.6%)
Height (cm)						
Mean	168.3		168.8		168.5	
Median (range)	170.0 (139.0– 185.4)		170.0 (131.0 – 190.0)		170.0 (131.0 – 190.0)	

Results Summary — Efficacy

The efficacy results are summarized for the ITT population in Table Error**! No text of specified style in document.**-4.

Time to progression

In total, 179 progression events in the ITT population were recorded based on an independent assessment and the median TTP under sorafenib + TACE was similar to the median TTP under placebo + TACE (169 versus 166 days). The impact of sorafenib + TACE treatment on TTP was statistically significant ($p = 0.072$) based on a stratified one-sided log-rank test ($\alpha = 0.15$). The hazard of disease progression was 20% lower for sorafenib + TACE compared with placebo + TACE, i.e, the hazard ratio was 0.797 (95% CI: 0.588, 1.080; 70% CI: 0.679, 0.936). This indicated a trend in favor of sorafenib + TACE over placebo + TACE; the 95% CI included unity.

Table Error! No text of specified style in document.**-4 Efficacy results in the ITT population**

	Placebo + TACE Median (95% CI) [70% CI]	Sorafenib + TACE Median (95% CI) [70% CI]	Comparison Log-rank test [1] (α = 0.15) p-value	Comparison Hazard ratio estimate (95% CI) [70% CI]
	N = 153 [3]	N = 154 [3]		
TTP per independent review	166 (113, 168) [156, 168]	169 (166, 219) [168, 172]	0.072	0.797 (0.588, 1.080) [0.679, 0.936]
TTP per Investigator's review	166 (114, 171) [158, 168]	180 (168, 225) [169, 223]	0.014	0.717 (0.523, 0.966) [0.613, 0.840]
OS [4]	n.d. (562, –) [2] [–, –] [2]	n.d. (554, –) [2] [616, –] [2]	0.295	0.900 (0.606, 1.330) [0.729, 1.105]
TTUP [4]	224 (158, 288) [168, 278]	95 (62, 113) [78, 111]	0.999	1.586 (1.200, 2.096) [1.368, 1.838]
TTVI/ES [4]	n.d. (–, –) [2] [–, –] [2]	n.d. (–, –) [2] [–, –] [2]	0.076	0.621 (0.321, 1.200) [0.438, 0.880]
	N = 153	N = 154		
CR+PR per independent review, n (%)	43 (28%)	55 (36%)		
Cochran-Mantel-Haenszel test[5]	p = 0.079			
CR+PR per Investigator's review, n (%)	53 (35%)	66 (43%)		
Cochran-Mantel-Haenszel test[5]	p = 0.068			
CR per independent review, n (%)	17 (11%)	20 (13%)		
CR per Investigator's review, n (%)	20 (13%)	21 (14%)		
PR per independent review, n (%)	26 (17%)	35 (23%)		
PR per Investigator's review, n (%)	33 (22%)	45 (29%)		

[1] Stratified by region and alpha-fetoprotein level at baseline
[2] Upper bound could not be estimated due to censored data
[3] For TTVI/ES: placebo + TACE with N= 152 , sorafenib + TACE with N = 153
[4] OS, TTUP and TTVI/ES were all based on Investigator's assessment
[5] α = 0.15; stratified by region and alpha-fetoprotein level
Abbreviations: CI – Confidence interval; CR – complete response; n.d. – not derivable; OS – Overall survival; PR – partial response; TTP – Time to progression; TTUP – Time to untreatable progression; TTVI/ES – Time to vascular invasion/extrahepatic spread.

In general, the results based on the Investigator's assessment were confirmative. Overall, 186 progression events in the ITT population were recorded and the median TTP under sorafenib + TACE treatment was prolonged by 14 days compared with the median TTP under placebo + TACE treatment (180 versus 166 days). The impact of sorafenib + TACE treatment on TTP was statistically significant ($p = 0.014$) based on a stratified one-sided log rank test ($\alpha = 0.15$). The hazard of disease progression was 28% lower for sorafenib + TACE compared with placebo + TACE, i.e., the hazard ratio was 0.717 (95% CI: 0.532, 0.966; 70% CI: 0.613, 0.840) indicating superiority of sorafenib over placebo as regards TTP.

The subgroup analyses of TTP in the ITT population based on an independent assessment showed clear trends (with the upper limit of the 95% CI below unity) favoring sorafenib + TACE over placebo + TACE for the subgroups planned dose received: <80% (0.42) and dose interruption: at least one (0.66) and in addition for the subgroups prior therapy: at least one (0.41) and duration of treatment: <12 weeks (0.27).

The subgroup analyses of TTP based on the Investigator's assessment confirmed trends favoring sorafenib + TACE treatment for almost all patient subgroups. Clear trends (with the upper limit of the 95% CI below unity) in favor of sorafenib + TACE were evident for the subgroups (hazard ratio) sex: female (0.28), age: <65 years (0.56), region: Asia (0.57), etiology of underlying disease: HBV (0.56), duration of treatment: ≥4 weeks (0.71), ≥12 weeks (0.70) and ≥24 weeks (0.66), bilirubin at baseline: normal (0.71), Child Pugh: grade 5 (0.67), planned dose received: <80% (0.53), and dose interruption: at least one (0.64).

The subgroup analyses of TTP showed for both assessments, independent and Investigator's assessment, commonly lowest hazard ratios for the following subgroups: Asia, at least one prior therapy, <12 weeks duration of treatment, normal bilirubin level at baseline, Child Pugh grade of 5, <80% of planned dose received, and best objective response other than CR or PR. A statistical intra-subgroup comparison was not performed.

Overall survival

In total, 101 death events in the ITT population were observed. The median for the analysis of overall survival was not reached. There was no statistically significant impact of sorafenib + TACE treatment over placebo + TACE treatment on OS ($p = 0.295$) based on a stratified one-sided log-rank test ($\alpha = 0.15$). The hazard ratio, i.e., the risk of death under sorafenib + TACE versus placebo + TACE, was 0.898 (95% CI: 0.606, 1.330), indicating a 10% decrease in hazard under sorafenib + TACE treatment, but the 95% CI of the hazard ratio estimate included unity.

The subgroup analyses of OS in the ITT population showed trends favoring sorafenib + TACE treatment for patients with sex: male (hazard ratio estimate 0.86), age: <65 years (0.63) and ≥75 years (0.61), and region: Asia (0.68) and Europe (0.92). A statistically significant impact of sorafenib + TACE treatment over placebo + TACE treatment on OS of patient subgroups based on a stratified one-sided log-rank test ($\alpha = 0.15$) was observed for age:<65 years ($p = 0.05$) and region: Asia ($p = 0.117$).

Time to untreatable progression

In total, 208 untreatable progression events in the ITT population were recorded based on the Investigator's assessment.

The median TTUP under sorafenib + TACE treatment was 95 days compared with 224 days under placebo + TACE treatment. The hazard for untreatable progression was 59% higher for

sorafenib + TACE compared with placebo + TACE. The hazard ratio was 1.586 (95% CI: 1.200, 2.096) indicating a clear trend in favor of placebo + TACE with the lower limit of the 95% CI being clearly above unity.

All subgroup analyses of TTUP in the ITT population based on the Investigator's assessment showed trends favoring placebo + TACE treatment for patients with sex: male (1.62) and female (1.38), age: <65 years (1.39), ≥65 to <75 years (1.79) and ≥75 years (1.43), region: Europe (1.51), Asia (1.42), America (6.28), and non-Asia (1.73).

Time to vascular invasion/extrahepatic spread

In total, 40 vascular invasion/extrahepatic spread events in the ITT population were recorded based on the Investigator's assessment. The median rate to vascular invasion/extrahepatic spread was not achieved in either treatment group. There was a statistically significant impact of sorafenib + TACE treatment ($p = 0.076$) on the time to vascular invasion/extrahepatic spread over placebo + TACE treatment based on a stratified one-sided log rank test ($\alpha = 0.15$).

The hazard of vascular invasion/extrahepatic spread was 38% lower for treatment with sorafenib + TACE compared with placebo + TACE, but the 95% CI of the hazard ratio estimate 0.621 (95% CI: 0.321, 1.200) included unity.

All subgroup analyses of the time to vascular invasion/extrahepatic spread with the variables sex, age and region in the ITT population based on the Investigator's assessment showed trends favoring sorafenib + TACE over placebo + TACE treatment. These patients subgroups were sex: male (hazard ratio estimate 0.76), age: <65 years (0.72) and ≥65 to <75 years (0.57), region: Europe (0.63), Asia (0.58), America (0.93), and non-Asia (0.67). No hazard ratio estimates could be derived for the subgroups sex: female and age: ≥75 years because no female patient ($n = 19$) and no patient ≥75 years experienced a vascular invasion or extrahepatic spread.

Best overall response rate

Based on an independent assessment the best overall response rate of 35.7% (95% CI: 28.2%, 43.8%) in the sorafenib + TACE group was higher than the response rate in the placebo + TACE group of 28.1% (95% CI: 21.1%, 35.9%). This difference was statistically significant ($p = 0.079$) applying a one-sided Cochran-Mantel-Haenszel test ($\alpha = 0.15$) stratified by region and AFP level at baseline. The beneficial effect observed for sorafenib + TACE treatment was confirmed by the Investigator's assessment ($p = 0.068$). A best overall response rate of 42.9% (95% CI: 34.9%, 51.1%) was obtained for the sorafenib + TACE group and of 34.6% (95% CI: 27.1%, 42.8%) for the placebo + TACE group based on the Investigator's assessment.

The results of PRO will be reported in a separately.

Results Summary — Safety

In the following discussion, all numbers in bold font are those results reported that have changed since the data cut-off date of 29 JUL 2011, while those in italic within the square brackets indicate the results up to that data cut-off date.

Overall there were only slight or no changes since the data cut-off date of 29 JUL 2011.

The exposure to study drug was lower in the sorafenib + TACE group compared with the placebo + TACE group. Median treatment durations for sorafenib and placebo were 21.0 weeks versus 27.3 weeks and the mean daily dose per cycle was **554.5 mg** [*557.1 mg*] versus a placebo equivalent dosage of **732.0 mg** [733.4 mg]. Within the sorafenib + TACE group, the median treatment duration was notably higher for Asian versus non-Asian patients: 30.0 weeks versus 17.4 weeks (unchanged since data cut-off date of 29 JUL 2011). The incidence of dose reductions and interruptions was higher in the sorafenib + TACE (**62.7%** [*60.8%*] and **87.6%** [*86.3%*]) than in the placebo + TACE group (**21.2%** [*20.5%*] and **72.8%** [*69.5%*]). More than 80% of dose reductions and interruptions required in the sorafenib + TACE group were due to AEs [*unchanged*].

Up to a maximum of 5 to 6 TACE procedures were conducted in both treatment groups. The proportions of patients who received ≥2 TACE procedures were lower in the sorafenib + TACE than in the placebo + TACE group. **Since the database cut-off date of 29 JUL 2011 up to 8 TACE procedures were conducted for one patient in the sorafenib + TACE group.**

The total number of TACE procedures performed in the placebo + TACE group was higher than in the sorafenib + TACE group. In the placebo + TACE group, TACE discontinuations in the Asian subpopulations were balanced, while in the non-Asian subpopulation more than twice as many patients in the sorafenib + TACE group received only one TACE procedure compared with the placebo + TACE group [*unchanged since data cut-off date*].

The overall incidence of treatment emergent adverse events (TEAEs) was similar between the sorafenib + TACE and placebo + TACE groups. At least one TEAE was reported for most patients during the clinical study: 152 (99.3%) patients in the sorafenib + TACE group and 143 (94.7%) patients in the placebo + TACE group [*unchanged since data cut-off date*]. There were more sorafenib/placebo-related TEAEs in patients treated with sorafenib + TACE than with placebo + TACE; 136 (88.9%) patients in the sorafenib + TACE group [*unchanged*] and **83 (55.0%) [***82 (54.3%)*] of patients in the placebo + TACE group.

The incidence of SAEs was higher in the sorafenib + TACE group than in the placebo + TACE group. This was also observed for SAEs considered to be related to sorafenib/placebo. There were **86 (56.2%)** [*84 (54.9%)*] patients in the sorafenib + TACE group and **56 (37.1%)** [*53 (35.1%)*] patients in the placebo + TACE group reporting SAEs and sorafenib/placebo relatedness was considered for 34 (22.2%) and 10 (6.6%) patients, respectively [*unchanged since data cut-off date*].

Most patients in both treatment groups experienced TEAEs of grade ≥3. The incidence rates of grade 3 and 4 TEAEs were notably higher in the sorafenib + TACE than in the placebo + TACE group: **50.3%** [*51.6%*] versus **38.4%** [*37.1%*] of the patients for grade 3 events and **24.8%** [*24.2%]* versus 11.9% [*unchanged*] for grade 4 events. The incidence of grade 5 TEAEs was similar between the treatment groups, **11.1%** [*9.2%*] versus **9.9%** [*9.3%*] of the patients, respectively.

Both, TEAEs leading to withdrawal or dose reduction of sorafenib/placebo were more frequent in the sorafenib + TACE group (**28.8% and 49.7%**) [*26.1% and 49.0%*] compared with the placebo + TACE group (17.9% and **13.2%** [*12.6%*]).

Deaths were reported at similar incidence in both treatment groups during the study: **47.1% versus 45.0%** [*34.0% versus 35.8%*], respectively. Deaths within 30 days of receiving last dose of study medication were reported for **10.5%** [9.2%] of the patients in sorafenib + TACE group and for **9.9%** [9.3%] in the placebo + TACE group.

The most frequent TEAEs (in ≥5% of patients in either treatment group) by CTCAE category showing similar or lower incidences under sorafenib versus placebo treatment were pain (74.5% in the sorafenib + TACE group versus 72.2% in the placebo + TACE group) [*unchanged since the data cut-off date*], neurology (**25.5% versus 23.2%**)[*24.2% versus 22.5%*], infection (**22.2%** versus **27.8%**) [*20.9% versus 26.5%*], renal/genitourinary events (**13.7%** [*11.8%*] versus 11.3%), vascular events (10.5% versus **9.3%** [*8.6%*]), syndromes (**9.2%** [*8.5%]* versus 9.9%), lymphatics (6.5% versus 10.6%) [*unchanged*], and musculoskeletal tissue events (**5.9%** [*5.2%*] versus 10.6%).

Treatment-emergent AEs by CTCAE category reported notably more frequently in the sorafenib + TACE than in the placebo + TACE group were gastrointestinal events (85.0% in the sorafenib + TACE group and **70.2%** [*69.5%*] in the placebo + TACE group), constitutional symptoms (71.2% versus 61.6%) [*no change since cut off*], dermatology/skin events (69.9% versus 31.1%) [*no change*], metabolic/laboratory events (**59.5%** versus **41.1%**) [*58.8% versus 40.4%*], general cardiac events (**35.9% versus 24.5%**) [*35.3% versus 22.5%*], pulmonary/upper respiratory events (30.1% versus **22.5%** [*21.9%*]), hepatobiliary/pancreas events(**24.2% versus 11.9%**) [*23.5% versus 11.3%*], hemorrhage/bleeding events(**23.5% versus 15.9%**) [*20.9% versus 14.6%*], blood/bone marrow events (**22.2%** [*20.9%*] versus 11.9%), and cardiac arrhythmia events (12.4% versus 6.6%) [*no change*].

Comparison of the most frequent TEAEs between treatment groups by CTCAE term (occurring in ≥10% of patients in either treatment group) showed overall similar or lower incidences under sorafenib versus placebo treatment for AEs such as abdominal pain NOS (**60.8%** [*60.1%*] versus 61.6%), fever (38.6% versus 34.4%) [*unchanged*], nausea (**38.6%** [*37.9%]* versus 39.1%), constipation (19.0% versus 17.9%) [*unchanged*], vomiting (18.3% versus **27.2%** [26.5%]), ascites (**19.0% versus 15.2%**) [*17.6% versus 13.9%*], ALT (17.0% versus 16.6%) [*unchanged*], cough (**13.7%** [*13.1%*] versus 8.6%), lipase (12.4% versus **9.3%** [*8.6%*]), insomnia (12.4% versus **15.2%** [*14.6%*]), pruritus (8.5% versus 11.9%) [*unchanged*], joint pain (8.5% versus 10.6%) [*unchanged*], hyperglycemia (5.2% versus 10.6%) [*unchanged*], and edema: limb (4.6% and 10.6%) [*unchanged*]. It is suggested that these events are mainly attributable to the underlying disease HCC and concomitant therapeutic procedures (TACE with DC bead plus doxorubicin).

Notably higher incidences under sorafenib versus placebo, suggesting that some relation to treatment cannot be excluded, were observed for the following TEAEs by CTCAE term: diarrhea (**53.6% versus 18.5%**) [*52.9% versus 17.2%*], hand-foot skin reaction (46.4% versus 6.6%) [*no change since cut-off*], fatigue (**43.8%** versus 33.1%) [*43.1% versus 33.1%*], anorexia(**31.4%** versus 20.5%) [*30.7% versus 20.5%*], hypertension (30.1% versus **17.9%**) [*30.1% versus 16.6%*], alopecia (28.1% versus 7.3%) [*unchanged*], AST elevation (24.8% versus 19.2%) [*unchanged*], rash/desquamation (21.6% versus 7.3%) [*unchanged*], weight loss (20.3% versus 10.6%) [*unchanged*], bilirubin – hyperbilirubinemia (16.3% versus 8.6%) [*unchanged*], hypoalbuminemia (12.4% versus 6.6%) [*unchanged*], muscle pain (11.8% versus **7.3%** [*6.6%*]), hemoglobin (11.1% versus 6.0%) [*unchanged*], oral mucositis (functional/symptomatic) (10.5% versus 4.0%)

[*unchanged*], liver dysfunction (**11.1% versus 4.0%**) [*10.5% versus 3.3%*], dry skin (10.5% versus 4.0%) [*unchanged*], platelets (**10.5%** versus 2.0%) [*9.8% versus 2.0%*], and hypokalemia (**10.5%** versus 2.6%) [*9.8% versus 2.6%*].

The most frequent grade 3 TEAEs showing a notably higher incidence in the sorafenib + TACE than in the placebo + TACE group were hypertension (16.3% versus **9.9%**) [*16.3% versus 9.3%*], bilirubin – hyperbilirubinemia (9.8% versus 2.6%) [*unchanged*], fatigue (9.8% versus 4.6%) [*unchanged*], hand-foot skin reaction (9.2% versus 1.3%) [*unchanged*], platelets (**7.8%** versus 1.3%) [*8.5% versus 1.3%*], lipase (7.2% versus **3.3%**) [*7.2% versus 2.6%*]. A grade 4 TEAE showing a notably higher incidence in the sorafenib + TACE than in the placebo + TACE group was elevation of AST (9.8% versus 4.0%) [*unchanged*].

The most frequent sorafenib/placebo-related TEAEs (≥5%) by CTCAE category with notably higher incidences in the sorafenib + TACE group were dermatology/skin (64.7% of patients in the sorafenib + TACE group versus 19.9% of patients in the placebo + TACE group) [*unchanged since cut-off date*], gastrointestinal events (59.5% versus 27.8%) [*unchanged since cut-off date*], constitutional symptoms (36.6% versus 24.5%) [*unchanged since cut-off date*], metabolic/laboratory events (24.8% versus 10.6%) [*unchanged*], cardiac general (19.6% versus **9.3%**) [*19.6% versus 8.6%*], hemorrhage/bleeding (**7.8%** versus 2.0%) [*7.2% versus 2.0%*], and hepatobiliary/pancreas events (5.2% versus 0%) [*unchanged since cut-off date*]. The most frequent sorafenib/placebo-related TEAEs by CTCAE term showing a clearly higher incidence in the sorafenib + TACE group included: hand-foot skin reaction (46.4% versus 6.6%) [*unchanged*], diarrhea (45.8% versus **10.6%**) [*45.8% versus 9.3%*], fatigue (**30.1%** versus **20.5%**) [*29.4% versus 19.9%*], alopecia (26.1% versus 6.6%) [*unchanged*], anorexia (20.3% versus 10.6%) [*unchanged*], rash/desquamation (19.6% versus 3.3%) [*unchanged*], hypertension (18.3% versus **7.9%**) [*18.3% versus 7.3%*], weight loss (13.1% versus 6.0%) [*unchanged*], dry skin (10.5% versus 3.3%) [*unchanged*], bilirubin - hyperbilirubinemia (9.2% versus 2.0%) [*unchanged*], oral cavity mucositis (functional/symptomatic) (7.8% versus 2.0%) [*unchanged*], lipase (7.2% versus 2.0%) [*unchanged*], and low platelets (5.2% versus 0%) [*unchanged*].

Gastrointestinal events were the most frequent TEAEs and reported with higher incidence in the sorafenib + TACE than in the placebo + TACE group: 85.0% versus **70.2%** [*85.0% versus 69.5%*]. Most events were of grade 1 or 2. Sorafenib/placebo-related gastrointestinal events were reported for 59.5% and 27.8% of the patients in the sorafenib + TACE and placebo + TACE groups [*unchanged since data cut-off date*]. Grade 3 and 4 events in the sorafenib + TACE group were notably more frequent in non-Asian versus Asian patients. Gastrointestinal events reported as SAEs occurred at higher incidence in the sorafenib + TACE than in the placebo + TACE group: 9.2% versus **4.6%** [*4.0%*]. Withdrawal of sorafenib/placebo due to gastrointestinal events occurred in **6 (3.9%)** [*5 (3.3%)*] patients versus 4 (2.6%) patients. The most common gastrointestinal events considered to be related to sorafenib/placebo and showing a higher incidence under sorafenib versus placebo were **diarrhea** (45.8% versus **10.6%** [*9.3%*]), **Anorexia** (20.3% versus 10.6%) [*unchanged*], **mucositis** (functional/symptomatic) of the oral cavity (7.8% versus 2.0%) [*unchanged*]. Frequent gastrointestinal TEAEs showing similar incidence rates between treatment groups, i.e. not revealing an apparent relation to treatment with sorafenib or placebo, were nausea (**38.6%** [*37.9%*] versus 39.1% of patients, and constipation (19.0% versus 17.9%) [*unchanged*].

Constitutional symptoms were frequently reported and with higher incidence in the sorafenib + TACE versus placebo + TACE group: 71.2% versus 61.6% [*unchanged*]. The majority of these events were of grade 1 or 2. Sorafenib/placebo-related constitutional symptoms were reported for

36.6% patients in the sorafenib + TACE group and for 24.5% in the placebo + TACE group [*unchanged*]. The most frequent constitutional symptoms considered to be related to sorafenib/placebo and showing a higher incidence under sorafenib versus under placebo were **Fatigue 30.1%** versus **20.5%** [*29.4% versus 19.9%*] and **weight loss** (13.1% versus 6.0%) [*unchanged*]. Both, fatigue and weight loss were overall more frequently reported in non-Asian than in Asian patients [*unchanged*].

Dermatologic/skin TEAEs were more frequently reported in the sorafenib + TACE than in the placebo + TACE group, 69.9% versus 31.1% [*unchanged*]. For most of these events sorafenib/placebo relatedness was considered, 64.7% versus 19.9%, respectively [*unchanged*]. The majority of these events were of grade 1 or 2 and grade 3 events were reported by 11.1% of patients in the sorafenib + TACE group and by 2.6% of patients in the placebo + TACE group. The most frequent dermatological symptoms considered to be related to sorafenib/placebo and showing a higher incidence under sorafenib versus placebo were **hand-foot skin reaction** (46.4% versus 6.6%) [*unchanged*], which were overall more often reported by Asian (66.1%) versus non-Asian patients (34.0%) [*unchanged*], **rash/desquamation** (19.6% versus 3.3%) [*unchanged*], **alopecia** 26.1% versus 6.6% [*unchanged*] showing a higher incidence rate in the sorafenib + TACE group for Asian (45.8%) versus non-Asian (17.0%) patients [*unchanged*], and **dry skin** (10.5% versus 3.3%) [*unchanged*].

Metabolic/laboratory events were more frequently reported in the sorafenib + TACE than in the placebo + TACE group: **59.5%** versus **41.1%** [*58.8% versus 40.4%*]. Sorafenib/placebo-relatedness was considered for 24.8% versus 10.6% of the patients, respectively [*unchanged*]. Overall, most of the events were of grade ≥3 with 9.2% versus 4.0% of the patients under sorafenib versus placebo reporting SAEs [unchanged]. Metabolic events leading to withdrawal of sorafenib/placebo was indicated in 7.2% and 6.0% of the patients of the sorafenib + TACE and placebo + TACE groups [*unchanged*]. Metabolic/laboratory events showing a higher incidence in the sorafenib + TACE than in the placebo + TACE group were **bilirubin – hyperbilirubinemia** (16.3% versus 8.6%) [*unchanged*], with a majority of events in the sorafenib + TACE group and few events in the placebo + TACE group considered to be related to sorafenib/placebo (9.2% versus 2.0%) [*unchanged*], **AST** elevations **(**24.8% versus 19.2%), mostly of grade ≥3 and considered not to be related to sorafenib/placebo [*unchanged*], and **hypokalemia** (**10.5%** [*9.8%*] versus 2.6%)

General cardiac events occurred more frequently in the sorafenib + TACE than in the placebo + TACE group: **35.9%** versus **24.5%** [*35.3% versus 22.5%*]. At least 50% of these events were grade ≥3 [*unchanged*]. Sorafenib/placebo-relatedness was considered for 19.6% of the patients in the sorafenib +TACE group and for **9.6%** [*8.6%*] of the patients in the placebo + TACE group. A general cardiac event reported more frequently in the sorafenib + TACE than in the placebo + TACE group was **hypertension** (30.1% versus **17.9%** [*16.6%*]). Most of these events were of grade 3 [*unchanged*]. Hypertension considered to be related to sorafenib/placebo were reported in 18.3% and **7.9%** [7.3%] of the patients, respectively.

Pulmonary/upper respiratory events occurred at higher incidence in the sorafenib + TACE than in the placebo + TACE group: 30.1% versus **22.5%** [*21.9%*]. Most of the events were of grade 1 or 2 [*unchanged*]. Two grade 5 events were reported, one in each treatment group [*unchanged*]. The higher incidence of pulmonary/upper respiratory events in the sorafenib + TACE group was due to the following TEAEs which occurred more frequently in the sorafenib + TACE group: cough (**13.7%** [*13.1%*] versus 8.6%), bronchial airway obstruction (2.0% versus 0%) [*unchanged*], dyspnea (**10.5%** [*9.8%*] versus 6.0%), and voice changes (5.9% versus 2.6%)

[*unchanged*]. A clear trend of the incidence in relation to treatment with the study medication was not evident [*unchanged*]. Most of the pulmonary/upper respiratory events in both treatment groups were considered not to be related to treatment with sorafenib/placebo [*unchanged*].

The incidence of **hepatobiliary/pancreas** events was higher in the sorafenib + TACE than in the placebo + TACE group: **24.2%** versus **11.9%** [*23.5% versus 11.3%*]. Sorafenib/placebo-relatedness was considered for 5.2% of the patients in the sorafenib + TACE group and for 0% of the patients in the placebo + TACE group [*unchanged*]. About 50% of the events were of grade 1 or 2 [*unchanged*]. Events classified as an SAE were reported in **13.1%** [*12.4%*] of the patients in the sorafenib + TACE versus 7.3% of the placebo + TACE patients; withdrawal of sorafenib/placebo occurred in **7.2%** [*6.5%*] of the sorafenib + TACE group versus 1.3% in the placebo + TACE group. Hepatobiliary/pancreas events of grade 5 occurred in **7 (4.6%)** [*6 (3.9%)*] patients in the sorafenib + TACE group and in 3 (2.0%) patients in the placebo + TACE group. These events comprised **liver dysfunction**/failure (**n = 9**) [*n=8*] and a hepatic renal syndrome (n = 1) [*unchanged*]. Liver dysfunction was more frequent in the sorafenib + TACE than in the placebo + TACE group: **11.1%** versus **4.0%** [*10.5% versus 3.3%*]. Most events were of grade ≥3 [*unchanged*]. Sorafenib/placebo relatedness was considered for 3.3% of the patients in the sorafenib + TACE group and for 0% of the patients in the placebo + TACE group [*unchanged*]. Liver dysfunction leading to withdrawal of sorafenib/placebo was reported for 3.9% of the patients in the sorafenib + TACE group and for no patients in the placebo + TACE group [*unchanged*]. Liver dysfunction was reported as an SAE was for **7.2%** [*6.5%*] versus **2.6%** [*2.0%*] of the patients under sorafenib versus placebo. **Pancreatitis** was reported with low and similar incidence rate for both treatment groups: 3.3% versus 2.0% [*unchanged*]. These events were all of grade 1 or 2, except one (0.7%) grade 4 event in the placebo + TACE group [*unchanged*].

The overall incidence of **hemorrhage/bleeding** events was higher in the sorafenib + TACE group than in the placebo + TACE group: **23.5% versus 15.9%** [*20.9% versus 14.6%*]. Sorafenib/placebo-relatedness was considered for **7.8%** [*7.2%*] versus 2.0% of the patients, respectively. Most hemorrhage/bleeding events were of grade 1 or 2 [*unchanged*].

Hemorrhage/bleeding events of grade 5 occurred in **3.3%** [*2.6%*] of the patients in the sorafenib + TACE group and in **2.6%** [*2.0%*] of the patients in the placebo + TACE group. All were gastrointestinal bleeding event which comprised: gastrointestinal (GI) hemorrhage - abdomen NOS (n = 2; n=1 with sorafenib, n=1 placebo [*unchanged*]), GI hemorrhage - esophageal varices (*n=1*,placebo *unchanged*), GI Hemorrhage - stomach (n = 1 sorafenib, [*unchanged*]), GI hemorrhage - lower GI NOS (n = 1 sorafenib) [*unchanged*], **GI hemorrhage peritoneal cavity (n=1 placebo; previously grade 4)**, GI hemorrhage - upper GI NOS (**n=2; n=1 sorafenib, n=1 placebo**) [*n = 1 placebo*], and hemorrhage with surgery (n = 1 sorafenib *unchanged*). An obvious treatment-related difference in the incidence of a hemorrhage/bleeding event (by term) between both treatment groups was not evident [*unchanged*].

Blood/bone marrow events were mostly of grade 3 and occurred more frequently in the sorafenib + TACE than in the placebo + TACE group: **22.2%** [*20.9%*] versus 11.9%. Sorafenib/placebo relatedness was reported for **11.1%** [*10.5%*] versus 6.6% of patients. The most frequent hematological TEAE reported was **anemia** (hemoglobin): 11.1% versus 6.0% [*unchanged*]. Most events were of grade 1 and 2 [*unchanged*]. Sorafenib/placebo relatedness was reported for 4.6% of the patients each in both treatment groups [*unchanged*]. **Thrombocytopenia** (platelets), mostly of grade 3, was more frequent in the sorafenib + TACE than in the placebo + TACE group: **10.5%** [*9.8%*] versus 2.0%. The incidence of thrombocytopenia in the sorafenib + TACE group was notably higher for Asian patients compared with non-Asian patients (**25.4%** [*23.7%*] versus

1.1%).

Cardiac arrhythmias occurred at higher incidence in the sorafenib + TACE than in the placebo + TACE group: 12.4% versus 6.6% [*unchanged*]. There was no specific pattern of a given type of arrhythmia, and the difference between the sorafenib + TACE and placebo + TACE groups for any specific type of arrhythmia was small, i.e., in the range of one to three patients [*unchanged*]. All events were of grade 1 or 2 and a relation to sorafenib/placebo was considered only for a minority of the events (3.3% versus 2.6%) [*unchanged*]. The arrhythmia events were distributed between atrial, nodal, and ventricular arrhythmias, suggesting no specific underlying mechanism [*unchanged*].

A **liver abscess** was reported by 2 patients receiving sorafenib + TACE and by 3 patients receiving placebo + TACE, all classified as liver infections (documented clinically). [unchanged].

Pain was a frequent AE (74.5% versus 72.2%), but a trend related to treatment was not evident [*unchanged*].

Treatment emergent AEs leading to death (grade 5) occurred at similar incidence in both treatment groups: in **17 (11.1%)** [*14 (9.2%)*] patients under sorafenib + TACE and in 14 (9.3%) patients under placebo + TACE. Grade 5 events by term which occurred more than once per treatment were liver dysfunctions, with higher incidence in the sorafenib + TACE than in the placebo + TACE group: **7 (4.6%)** [*6 (3.9%)*] versus 2 (1.3%) patients. Death not associated with CTCAE term – disease progression NOS was reported for 1 (0.7%) patient in the sorafenib + TACE group and for 2 (1.3%) patients in the placebo + TACE group [*unchanged*].

All other TEAEs leading to death were singular grade 5 events per treatment group [*unchanged*]. For the sorafenib + TACE group unique events included constitutional symptoms – other (specify), gastrointestinal hemorrhage/bleeding of the stomach, hemorrhage/bleeding of the lower gastrointestinal region, hemorrhage with surgery, pulmonary – other (specify), syndromes – other, and **infection (documented clinically) lung (pneumonia)[since data cut-off date 29 JUL 2012].**

Unique for the placebo + TACE group included were gastrointestinal hemorrhage/bleeding of esophageal varices, hepatobiliary - other (specify), cardiac ischemia - infarction, cardiac general – other (specify), death not associated with CTCAE term - multi-organ failure, death not associated with CTCAE term – sudden death, duodenum perforation, infection with unknown absolute neutral count (ANC) - pancreas (n = 2), and pneumonitis.

Hemorrhage - gastrointestinal, upper gastrointestinal NOS occurred both in the placebo + TACE group and the sorafenib + TACE group [update since data cut-off on 29 JUL 2011]. Hemorrhage/bleeding of the upper gastrointestinal region occurred in single cases in both treatment groups [*unchanged since cut-off date*].

Treatment-emergent SAEs were more frequently reported in the sorafenib + TACE than in the placebo + TACE group: **56.2%** [*54.9%*] versus **37.1% [***35.1%*]. Most SAEs were not related to sorafenib/placebo treatment [*unchanged*]; the incidence rates for treatment-emergent SAEs considered to be related to sorafenib/placebo were 22.2% versus 6.6% [*unchanged*]. The most frequent treatment-emergent SAEs by CTCAE category with higher incidence in the sorafenib + TACE than in the placebo + TACE group were: hepatobiliary/pancreas events (**13.1%** [*12.4%*] versus 7.3%), metabolic laboratory events (9.2% versus 4.0%) [*unchanged*], gastrointestinal events (**9.8%** versus **4.6%**) [9.2% versus 4.0%], and neurology (5.2% versus 0.7%) [*unchanged*].

The most frequent treatment-emergent SAEs by term showing a higher incidence in the sorafenib + TACE group compared with the placebo + TACE group (≥3%) are liver dysfunction **7.2%**

versus 2.6% [*6.5% versus 2.0%*], AST (4.6% versus 0%) [*unchanged*], ALT (3.9% versus 0%) [*unchanged*], and encephalopathy (3.9% versus 0.7%) [*unchanged*].

Patients reporting TEAEs leading to dose reduction of sorafenib/placebo were clearly more frequent in the sorafenib + TACE than in the placebo + TACE group (**49.7% versus 13.2%)** [*49.0% versus 12.6%*]. The most frequent TEAEs by CTCAE term leading to dose reduction with notably higher incidence in the sorafenib + TACE group were: hand-foot skin reaction (17.6% versus 0%), diarrhea (6.5% versus 0%), rash/desquamation events (5.9% versus 0%), low platelets (5.2% versus 0%), fatigue (3.9% versus 0%), lipase (3.9% versus 0%), bilirubin - hyperbilirubinemia (4.6% versus 2.6%) [*all unchanged since data cut-off date*].

Patients reporting TEAEs leading to withdrawal of sorafenib/placebo were more frequent in the sorafenib + TACE than in the placebo + TACE group(**28.8%** [*26.1%*] versus 17.9%). The most frequent TEAEs by CTCAE term leading to withdrawal of sorafenib/placebo with higher incidence in the sorafenib + TACE group were liver dysfunction (3.9% versus 0%) [*unchanged*], platelets (**2.0%** [*1.3%*] versus 0%), hand-foot skin reaction (1.3% versus 0%) [*unchanged*], and bilirubin – hyperbilirubinemia (2.6% versus 1.3%) [*unchanged*].

Frequent laboratory abnormalities of grade 3 and observed at similar incidence in both treatment groups included AST elevations, ALT elevations, lymphopenia, hyponatremia and amylase. Also frequent, but showing a clearly higher incidence in the sorafenib + TACE than in the placebo + TACE group were hypophosphatemia (44.4% versus **20.7%** [19.3%]), bilirubin - hyperbilirubinemia (17.0% versus 6.0%) [*unchanged*], and low platelet counts (**13.7%** [*14.4%*] versus 3.3%), and hypokalemia (**9.8%** [*9.2%*] versus 2.7%). Grade 4 laboratory abnormalities with a slightly higher incidence under sorafenib + TACE compared with placebo + TACE treatment were: AST elevations (13.1% versus 8.0%) [*unchanged*], ALT elevations (6.5% versus 4.0%) [*unchanged*], and lipase (13.7% versus **10.7%** [*10.0%*]).

For patient number 540290022 whose treatment was still ongoing, no AEs were reported since the data cut-off date (29 AUG 2012). This patient was reported to have had an overall compete response reported on 4 FEB 2013. This response status had been maintained since 13 DEC 2010.

Other evaluations

The patient reported outcome (PRO) results and the results of the biomarker analyses that were based on the data collected from 30 MAR 2009 until 29 JUL 2011 are presented in a separate report.

The PRO endpoints of health-related quality of life (HRQoL), hepatobiliary cancer symptom, and general health status as measured by the FACT-L, its subscale LCS, and EQ-5D, respectively, were similar between the treatment groups at baseline. The treatment effect was statistically significant in favor of placebo in the mixed linear model and area under the curve (AUC) analysis conducted, however, the difference was not clinically meaningful based on the clinically important differences (minimally important difference of 8-9 points in the total FACT-Hep, 5-6 points in the Hepatobiliary Cancer Subscale (HCS), 0.07 to 0.12 points on the EQ-5D index and a change of 7 to 12 points on the visual analog scale (VAS) established by Steel et al. (4) and Pickard et al. (3). The median time to symptomatic deterioration was 312 days (95% CI: 227, 366) for the TACE + placebo group and 225 days (95% CI: 168, 314) for the TACE + sorafenib group. The estimated hazard ratio was 1.1632 (95% CI: 0.8124, 1.6654), and was not statistically significant (p=0.795).

Biomarker results will be presented separately from this report.

Conclusion(s)

The study met its primary endpoint of improvement in TTP when sorafenib was added to a regimen of TACE with DC Bead and doxorubicin in intermediate stage HCC patients with p = 0.072 by a one-sided alpha of 0.15 and a HR of 0.797 (95% CI: 0.588, 1.080).

In the secondary endpoint analyses, there was a statistically significant benefit on the time to vascular invasion/extrahepatic spread in the sorafenib treatment arm (p = 0.076; HR = 0.621 [95% CI: 0.321, 1.200]). No statistically significant impact of sorafenib treatment was observed for OS. The observed inferior TTUP for patients treated with sorafenib versus placebo could probably be attributable to a higher proportion of patients not receiving more than one or two TACE administrations in the sorafenib arm, due to adverse events or protocol-defined contraindications to the TACE procedure. Greater efficacy (TTP, OS) was observed in the stratified group of Asian patients (compared with patients from Western countries). This may have been due to longer sorafenib treatment duration in Asian patients than in Non-Asian patients, as the number of TACE treatments was balanced between the treatment groups in Asia compared to Western countries. The combination of sorafenib plus TACE was technically feasible and well tolerated, with an overall safety profile consistent with that known for sorafenib and TACE.

Overall it can be said that the results confirmed that the combination of sorafenib plus TACE was technically feasible and well tolerated, with an overall safety profile consistent with that known for sorafenib and TACE.

Altogether no benefit was seen for sorafenib +TACE treatment compared placebo +TACE in terms of the PRO endpoints for the HRQOL assessment.

Publication(s):	None		
Date Created or Date Last Updated:	12 Jan 2014	Date of Cinical Study Report:	15 Nov 2013

Investigational Site List

Marketing Authorization Holder in Germany	
Name	**Bayer Vital GmbH**
Postal Address	**D-51368 Leverkusen** **Germany**
Sponsor in Germany (if applicable)	
Legal Entity Name	**Bayer Pharma AG**
Postal Address	**D-51368 Leverkusen** **Germany**

List of Investigational Sites

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
1	Dr. Paul Gow	Austin Health	Gastroenterology & Liver Transplant Unit Level 8, Harold Stokes Building Austin Health Studley Road	3084	Heidelberg	AUSTRALIA
2	Prof Darrell Crawford	Greenslopes Private Hospital	Gallipoli Medical Research Centre Clinical Trials Unit Greenslopes Private Hospital 121 Newdegate Street	4120	Greenslopes	AUSTRALIA
3	Prof. William Sievert	Monash Medical Centre	Department of Medicine Level 5, E Block, 246 Clayton Road	3168	Clayton	AUSTRALIA
4	Professor Simone Strasser	Royal Prince Alfred Hospital	AW Morrow Gastroenterology & Liver Centre Level 9, Building 75 Missenden Road	2050	Camperdown	AUSTRALIA
5	Prof. Gary Jeffrey	Sir Charles Gairdner Hospital	Western Australian Liver Transplantation Service Sir Charles Gairdner Hospital G Block, 6th Floor, Hospital Avenue	6009	Nedlands	AUSTRALIA
6	Assoc. Prof. Stuart Roberts	The Alfred Hospital	Gastroenterology Department. Level 4, Ward B, Main Ward Block, 55 Commercial Road	3004	Melbourne	AUSTRALIA

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
7	Prof. Dr. Markus Peck-Radosavljevic	Allgemeines Krankenhaus der Stadt Wien Universitätskliniken	Medical Oncology Dept Block 4, Building 37 Pacific Highway	1090	Wien	AUSTRIA
8	Prof. Dr. Wolfgang Vogel	Universitätsklinikum Innsbruck	AW Morrow Gastroenterology & Liver Centre Level 9, Building 75 Missenden Road	6020	Innsbruck	AUSTRIA
9	Prof. Jean DELWAIDE	CHU de Liège	Service Gastro-entérologie/Hépatologie Domaine Universitaire du Sart Tilman Bâtiment B35	4000	LIEGE	BELGIUM
10	Dr. Ivan BORBATH	CU Saint-Luc/UZ St-Luc	Service de Gastro-Entérologie/Dienst Gastro-Enterologie Avenue Hippocrate 10 Hippocrateslaan	1200	BRUXELLES - BRUSSEL	BELGIUM
11	Prof. Dr. Jean-Luc VAN LAETHEM	Hôpital Erasme/Erasmus Ziekenhuis	Service Gastro-Entérologie/Dienst Gastro-Enterologie Route de Lennik 808 Lenniksebaan	1070	BRUXELLES - BRUSSEL	BELGIUM
12	Prof. Dr. Chris VERSLYPE	UZ Leuven Gasthuisberg	Interne Geneeskunde - Lever-Galblaas-Pancreas CDG Gebouw, bordeaux, 4de verdiep Herestraat 49	3000	LEUVEN	BELGIUM
13	Dr. Kevork Peltekian	Queen Elizabeth II Health Sciences Centre	1278 Tower Road VG Site - Room 6-302	B3H 2Y9	Halifax	CANADA
14	Dr. Morris Sherman	Toronto General Hospital-University Health Network	585 University Avenue NCSB 11C-1252	M5G 2N2	Toronto	CANADA
15	Dr. Kelly Burak	University of Calgary	Heritage Medical Research Clinic Room 6D35, TRW Bldg 3350 Hospital Drive NW	T2N 4N1	Calgary	CANADA
16	Prof Guohong Han	1st Affiliated Hosp., 4th Military Med Univ.	Department of Digestive Interventional Radiology First Affiliated Hospital of Fourth Military medical University No.15 West Changle Rd.,	710032	Xi'an	CHINA
17	Prof Renjie Yang	Beijing Cancer Hospital	Interventional Therapy Department,No.52 Fucheng Road Haidian District	100142	Beijing	CHINA

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
18	Prof Jinwan Wang	Beijing Cancer Institute&Hospital CAMS	Department of Medical Oncology Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS) No.17 Panjiayuan Nanli.	100021	Beijing	CHINA
19	Prof Jiamei Yang	Shanghai Eastern Hepatobiliary Surgery Hospital	Shanghai Eastern Hepatobiliary Surgery Hospital Hepatobiliary Surgery Department,No.225,Changhai Road	200438	Shanghai	CHINA
20	Prof Peihong Wu	Sun Yat-Sen University Cancer Center	The Department of Medical Imaging and Interventional Radiology Cancer Center No.651, Dongfengdong Road	510060	Guangzhou	CHINA
21	Prof Jianhua Wang	Zhongshan Hospital Fudan University.	Radiology Department,No.180, Fenglin Road	200032	Shanghai	CHINA
22	Professeur Jean-Pierre BRONOWICKI	Centre Hospitalier Universitaire Brabois	CHU de Nancy Hopital Brabois adultes Service d'Hépato-gastroentérologie Rue du Morvan	54500	VANDOEUVRE-LES-NANCY	FRANCE
23	Pr. Jean-François SEITZ	C.H.U. Timone	CHU la Timone Service d'hepatologie et d'oncologie 246 rue Saint Pierre	13005	Marseille	FRANCE
24	Pr. Philippe MATHURIN	Hôpital Claude Huriez - Lille	C.H.R.U. Hôpital Claude Huriez Service des maladies de l'appareil digestif Place de Verdun	59000	LILLE	FRANCE
25	Dr Thomas DECAENS	Hôpital Henri Mondor - Créteil	Hôpital Henri Mondor Service d'Hépato-gastroentérologie 51, avenue de Lattre de Tassigny	94010	CRETEIL	FRANCE
26	Pr. Didier SAMUEL	Hôpital Paul Brousse - Villejuif	Hôpital Paul Brousse Département hépato-biliaire 12, avenue Paul Vaillant	94800	VILLEJUIF	FRANCE
27	Pr. Olivier ROSMORDUC	Hopital Saint Antoine - Paris	Hopital Saint Antoine Service d'Hépato-gastroentérologie (orienté hépatologie) du Pr Poupon 184, rue du Faubourg Saint Antoine	75571	PARIS	FRANCE

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
28	Docteur Jean-Didier GRANGE	Hôpital Tenon - Paris	Hôpital Tenon Service d'hépato-gastroentérologie 4, rue de Chine	75020	PARIS	FRANCE
29	Prof Jérome DUMORTIER	Hospital Edouard Herriot	Hospital Edouard Herriot Batiment H - 2 ème etage 1, Place Arsonval	69003	Lyon	FRANCE
30	Pr. Philippe MERLE	Hôtel Dieu - Lyon Cedex	Hospices Civils de Lyon Hôpital Hôtel Dieu Service Hépato-gastroentérologie 1, place de l'Hôpital	69288	LYON CEDEX	FRANCE
31	Prof Michel DUCREUX	Institut Gustave Roussy	Service de Gastroentérologie 39 rue Camille-Desmoulins	94805	VILLEJUIF	FRANCE
32	Hr. Prof. Dr. Peter Galle	Johannes-Gutenberg-Universität Mainz	I. Medizinische Klinik und Poliklinik Langenbeckstr. 1	55131	Mainz	GERMANY
33	Hr. Dr. Stefan Pluntke	Kliniken Essen - Mitte	Evang. Huyssens-Stiftung Klinik für Innere Medizin IV Internistische Onkologie/Hämatologie Henricistr. 92	45136	Essen	GERMANY
34	Hr. Prof. Dr. Jörg Trojan	Klinikum der Johann Wolfgang Goethe Universität Frankfurt	Medizinische Klinik II Abteilung f. Gastroenterologie, Hepatologie Theodor-Stern-Kai 7	60590	Frankfurt	GERMANY
35	Hr. PD Dr. Frank Kolligs	LMU Klinikum der Universität München - Großhadern	Medizinische Klinik und Poliklinik II Marchioninistraße 15	81377	München	GERMANY
36	Hr. PD Dr. Deike Strobel	Universität Erlangen-Nürnberg	Medizinische Klinik I mit Poliklinik Ulmenweg 18	91054	Erlangen	GERMANY
37	Hr. Prof. Dr. Frank Lammert	Universitätskliniken des Saarlandes	Klinik für Innere Medizin II Gastroenterologie, Hepatologie, Endokrinologie, Diabetologie Kirrberger Str. 1	66421	Homburg	GERMANY
38	Hr. Prof. Dr. Guido Gerken	Universitätsklinikum Essen	Medizinisches Zentrum Klinik für Gastroenterologie und Hepatologie Hufelandstr. 55	45122	Essen	GERMANY

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
39	Hr. Prof. Dr. Hubert Blum	Universitätsklinikum Freiburg	Abteilung für Innere Medizin II Hugstetter Str. 55	79106	Freiburg	GERMANY
40	Hr. Dr. Henning Wege	Universitätsklinikum Hamburg Eppendorf (UKE)	Zentrum für Innere Medizin I. Medizinische Klinik und Poliklinik Martinistr. 52	20246	Hamburg	GERMANY
41	Hr. Prof. Dr. Tom Ganten	Universitätsklinikum Heidelberg	Centrum für Tumorerkrankungen (NCT) Heidelberg Im Neuenheimer Feld 460	69120	Heidelberg	GERMANY
42	Hr. Prof. Dr. Harald Schmidt	Universitätsklinikum Münster	Klinische und Experimentelle Transplantationshepatologie Domagkstr. 3a	48149	Münster	GERMANY
43	Fr. Dr. Sylvia Schneider	Universitätsklinikum Regensburg	Klinik und Poliklinik für Innere Medizin I Franz-Josef-Strauss-Allee 11	93042	Regensburg	GERMANY
44	Prof. Fabio Farinati	A.O. di Padova	Gastroenterologia Dip. Scienze Chirurgiche e Gastroenterologiche Via Giustiniani, 2	35128	Padova	ITALY
45	Prof. Luigi Bolondi	A.O.U. di Bologna	Medicina Interna Dip. Malattie Apparato Digerente e Medicina Interna Policlinico S.Orsola-Malpighi Via Albertoni, 15	40138	Bologna	ITALY
46	Prof. Alfredo Guglielmi	A.O.U. Integrata Verona	Chirurgia Generale A - Vascolare DAI Chirurgia ed Oncologia - Pancreas Center Policlinico G.B. Rossi (Borgo Roma) Piazzale L. Scuro, 10	37134	Verona	ITALY
47	Prof. Riccardo Lencioni	A.O.U. Pisana	Diagnostica Interventistica Epatologica Dip.Trapiantologia Epatica-Epatologia-Infettivologia S.O. Cisanello Via Paradisea, 2	56124	Pisa	ITALY
48	Prof. Mario Rizzetto	A.O.U. San Giovanni Battista	Gastroepatologia Corso Bramante, 88	10126	Torino	ITALY

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
49	Prof. Adolfo Francesco Attili	Azienda Policlinico Umberto I	Gastroenterologia ed Endoscopia Digestiva Dip. Medicina Clinica Viale dell'Università, 37	00185	Roma	ITALY
50	Dr. Sergio Petronelli	Ente Ecclesiastico Ospedale Generale Regionale Miulli	Angiografia e Radiologia Interventistica Strada Provinciale 127 Acquaviva-Santeramo Km 4,1	70021	Acquaviva delle Fonti	ITALY
51	Prof. Massimo Colombo	IRCCS Fond. Ca' Granda Ospedale Maggiore Policlinico	Gastroenterologia 1 Dip. Malattie Apparato Digerente ed Endocrinometabolico Via Francesco Sforza, 35	20122	Milano	ITALY
52	Dr. Vincenzo Mazzaferro	IRCCS Istituto Nazionale Tumori	Chirurgia Generale 1 (Epato-gastro-pancreatica) e Trapianto di Fegato Dip. Chirurgia Via G.Venezian, 1	20133	Milano	ITALY
53	Dr. Angelo Luca	ISMETT Ist Mediterraneo Trapianti e Terapie alta spec	Radiologia Diagnostica ed Interventistica Via E. Tricomi, 1	90127	Palermo	ITALY
54	Dr. Won-Young Tak	Kyungpook National University Hospital	Kyungpook National University Hospital 200 Dongduk-ro Jung-gu	700-721	Daegu	KOREA, REPUBLIC OF
55	Dr Seung-Woon Paik	Samsung Medical Center	Division of Gastroenterology Department international medicine, Samsung Medical Center 50 Irwon-dong Gangnam-gu	135-710	Seoul	KOREA, REPUBLIC OF
56	Dr. Jung-Hwan Yoon	Seoul National University Hospital	101 Daehak-ro Jongno-gu	110-744	Seoul	KOREA, REPUBLIC OF
57	Dr. Sang Hoon Ahn	Severance Hospital, Yonsei University College of Medicine	Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Yonsei University Health System 250 Seongsanno Seodaemun-gu	120-752	Seoul	KOREA, REPUBLIC OF
58	Dr. Su Pin Choo	National Cancer Center	National Cancer Centre Department of Medical Oncology, Level 3, 11 Hospital Drive	169610	Singapore	SINGAPORE
59	Dr. Luis Castells	Ciutat Sanitària i Universitaria de la Vall d'Hebron	Unitat d'Hepatologia Passeig de la Vall d'Hebrón, 119-129	08035	Barcelona	SPAIN

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
60	Dra. Mercedes Vergara	Corporació Sanitària Parc Taulí	Departamento de Hepatología Edificio Taulí, Planta 8	08208	Sabadell	SPAIN
61	Dra. María Varela	Hospital Central de Asturias	Servicio Digestivo Edificio Residencia 6ª planta C/.Celestino villamil s/n	33006		SPAIN
62	Dr. Alejandro Forner	Hospital Clínic i Provincial de Barcelona	Servicio de Oncología Médica C/ Villarroel, 170	08036	Barcelona	SPAIN
63	Dr. Javier Fernández	Hospital Clínico Universitario de Santiago de Compostela	Servicio de Digestivo A Choupana, s/n	15706	Santiago de Compostela	SPAIN
64	Dr. Javier Bustamante Schneider	Hospital de Cruces	Servicio de Oncología Pza. de Cruces, s/n	48903	Cruces/Barakaldo	SPAIN
65	Dr. Javier Irurzun	Hospital General Universitario de Alicante	Servicio de Radiodiagnóstico c/ Pintor Baeza, s/n	03010	Alicante	SPAIN
66	Dra. Carmen González	Hospital General Universitario de Valencia	Servicio Aparato Digestivo Avda Tres Cruces, s/n Edificio Izquierdo, 3ra. planta	46014	Valencia	SPAIN
67	Dr. Luís Ruíz del Arbol	Hospital Ramón y Cajal	Servicio de Gastroenterología Consultas Externas, planta -1 Ctra. de Colmenar, Km. 9,1	28034	Madrid	SPAIN
68	Dra. Pilar Barrera	Hospital Reina Sofía	Unidad Hepática Edificio de Consultas Externas, 1ª planta-izq. Avda. Menéndez Pidal, s/n	14004	Córdoba	SPAIN
69	Dr. Ramón Planas	Hospital Universitari Germans Trias i Pujol	Unidad Hepática. Servicio Digestivo Ctra. del Canyet, s/n	08916	Badalona	SPAIN
70	Dr. Enrique Quintero	Hospital Universitario de Canarias	Servicio de Digestivo c/ Ofre, s/n. La Cuesta	38320	La Laguna	SPAIN
71	Dr. Juan Manuel Pascual	Hospital Universitario "La Paz"	Paseo de la Castellana, 261	28046	Madrid	SPAIN
72	Dr. Shun-Sheng Wu	Changhua Christian Hospital	Department of Gastroenterology Changhua Christian Hospital, Basement 1 No. 135, Nan-Hsiao Street, Clinical Trial Center	500		TAIWAN
73	Dr. Pei-Jer Chen	National Taiwan University Hospital	National Taiwan University Hospital No 7 Chung-Shan South Road,	10016	Taipei	TAIWAN

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
74	Dr Gar-Yang Chau	Veterans General Hospital	Taipei Veterans General Hospital No.201, Shih-Pai Road, Section 2	11217	Taipei	TAIWAN
75	Dr. Natalie Bzowej	California Pacific Medical Center	Division of Gastroenterology/Hepatology Department of Transplantation - 3rd Floor 2340 Clay Street	94115	San Francisco	UNITED STATES
76	Dr. Nikolaos Pyrsopoulos	Florida Hospital Orlando	Liver Transplant/Hepatology Services 2501 N. Orange Avenue Suite 514	32804	Orlando	UNITED STATES
77	Dr. Douglas Heuman	Hunter Holmes McGuire Veterans Affairs Medical Center	GI (111N) 1201 Broad Rock Boulevard	23249	Richmond	UNITED STATES
78	Dr. Sasan Roayaie	Mount Sinai Medical Center	One Gustave L. Levy Place	10029	New York	UNITED STATES
79	Dr. Paul Bloomston	Ohio State University Medical Center	Starling-Loving Hall 320 West 10th Avenue	43210-1240	Columbus	UNITED STATES
80	Dr. Willscott Naugler	Oregon Health and Science University	3181 SW Sam Jackson Park Road Mail Code L106-RI	97239	Portland	UNITED STATES
81	Dr. Marty Sellers	Piedmont Hospital	1968 Peachtree Road NW	30309-1231	Atlanta	UNITED STATES
82	Dr. Alex Befeler	St. Louis University Hospital	GI & Hepatology Clin Res Unit 2nd Floor 3545 Lafayette Avenue	63104	St. Louis	UNITED STATES
83	Dr. Ron Cabrera	University of Florida-Gainesville	Hepatology Department 1600 SW Archer Road Room M-440	32610-0316	Gainesville	UNITED STATES
84	Dr. Lynn Feun	University of Miami Hospital	1475 NW 12th Avenue	33136	Miami	UNITED STATES
85	Dr. Thomas Malpass	Virginia Mason Medical Center	Department of Hematology-Oncology 1100 Ninth Ave MS C2-HEM	98101	Seattle	UNITED STATES

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Nexavar
Brand/Trade Name(s) ex-US	Nexavar
Generic Name	Sorafenib
Main Product Company Code	BAY43-9006
Other Company Code(s)	BAY54-9085
Chemical Description	**(1)** 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-**(2)** 4-(4-{3.[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N2-methylpyridine-2-carboxamide
Other Product Aliases	Sorafenib tosylate

Date of last Update/Change: 28 Apr 2012