Clinical Study Synopsis

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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 AG	
Study Number:	12006	NCT00449033
Study Phase:	III	
Official Study Title:	A phase III randomized, double-blind, placebo-controlled trial comparing the efficacy of gemcitabine, cisplatin and sorafenib to gemcitabine, cisplatin and placebo in first-line treatment of patients with Stage IIIb with effusion and Stage IV non-small cell lung cancer (NSCLC)	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Sorafenib (Nexavar, BAY43-9006) +GC	
Name of Active Ingredient:	Sorafenib in combination with gemcitabine/cisplatin (GC)	
Dose and Mode of Administration:	Sorafenib 400 mg (2 tablets of 200 mg) twice daily (bid) administered orally Gemcitabine 1250 mg/m^2 intravenous (IV) on Days 1 and 8 Cisplatin 75 mg/m^2 IV on Day 1	
Reference Therapy/Placebo		
Reference Therapy:	Placebo in combination with gemcitabine/cisplatin	
Dose and Mode of Administration:	Two tablets bid of matching placebo were administered orally. Gemcitabine 1250 mg/m^2 IV on Day 1 and 8 Cisplatin 75 mg/m^2 IV on Day	
Duration of Treatment:	Each treatment cycle consisted of 21 days. Subjects received sorafenib/placebo tablets bid in combination with gemcitabine and cisplatin (GC) for up to 6 cycles in the Chemotherapy Phase. If the subject had radiological evidence of stable disease (SD) or better after completing up to 6 cycles in the Chemotherapy Phase, he/she could continue to the Maintenance Phase. During the Maintenance Phase, the subject received daily sorafenib/placebo tablets until the criteria for withdrawal were met.	
Studied period:	Date of first subjects' first visit:	22 FEB 2007
	Date of last subjects' last visit:	13 JUN 2011
Premature Study Suspension / Termination:	No	

Substantial Study Protocol Amendments:	Amendment no. 1 (dated 31 OCT 2006) was applicable to all countries. It specified the following changes: • Radiological assessments were performed every 6 weeks +/- 5 days (after the first dose of study drug). • In the Chemotherapy Phase, dose reductions on Day 1 were permanent while on Day 8, dose reductions of gemcitabine were not permanent. • Hematology analysis on Day 1 of each cycle during the Maintenance phase was changed to include red blood cells (RBC), hemoglobin, hematocrit, platelet count, and white blood cells (WBC). WBC was to include absolute counts for differential neutrophil (or granulocytes) and lymphocytes. Amendment no. 2 (dated 08 JAN 2007) was locally valid for centers in Germany only. Subjects with hearing impairment were excluded from the study because cisplatin is contraindicated in these subjects. Amendment no. 3 (dated 19 JAN 2007) was locally valid for centers in France only. The timeframe between gemcitabine and cisplatin administration and radiotherapy was extended to 4 weeks. Amendment no. 4 (dated 24 OCT 2007) was applicable to all countries. Overall survival (OS) was added as the major additional primary variable. Other changes specified were: • The number of subjects was increased to 900. The enrollment time was increased to 17.5 months and overall study duration to 29.5 months. • Serum creatinine clearance limit was added to the inclusion criteria. • No blood sample for the plasma biomarker evaluations was required at end of treatment visit. • Progression-free survival (PFS) analysis was to be performed when approximately 526 PFS events were observed. • A DMC was to be instituted for independent review of efficacy and safety data. In addition to the final analyses of OS and PFS, one formal interim analysis of OS was planned during the study. The interim analysis of OS was to be performed at the time of the formal analysis of PFS (at approximately 526 events). Details of the statistical analysis were provided. Amendment no. 5 (dated 31 JAN 2008) was applicable to all countries. The radiological assessment was clarified (CT scans of the complete chest were required), to decouple the efficacy boundary and the futility boundary for the planned formal interim analysis of OS, the two boundaries were made independent of each other and the interim analysis of OS was modified according to this rationale. Amendment no. 6 (dated 04 APR 2008) was applicable to all countries. Subjects with squamous cell histology were excluded from the trial [subjects with Stage IIIB (with effusion) or Stage IV NSCLC of non-squamous cell carcinoma subtype were included]. Amendment no. 7 (dated 17 JUL 2008) was applicable to all countries. The primary and secondary efficacy analyses on non-squamous subjects were outlined, since recruitment of squamous subjects had

	been prematurely terminated. OS was retained as the only primary variable (i.e., PFS was considered a secondary endpoint) and two planned futility interim analyses of OS were specified and the efficacy interim analysis originally planned was removed.
Study Centre(s):	The study was conducted at 93 centers in 16 countries: Germany (12 centers), Italy (12), France (11), Spain (9), China (8), Belgium (6), Brazil (6), the United Kingdom (6), Israel (5), the Netherlands (5), Finland (3), Mexico (3), Austria (2), Greece (2), Switzerland (2), and Cyprus (1).
Methodology:	This is a randomized, double-blind, placebo controlled study. Overall survival: All randomized subjects were followed for survival information. After discontinuation of study drug treatment, subjects continued to the Post-treatment Follow-up Period and were contacted every 3 months until death was recorded. Tumor response and disease progression assessments using Response Evaluation Criteria in Solid Tumors (RECIST) (v. 1.0) were based on a blinded review of computed tomography (CT) scans of the chest and abdomen. Non-target lesions were also recorded. In addition to Investigator-assessments, independent centralized radiological assessments were performed for approximately half of the subjects. Radiological assessments were performed at screening, and every 6 weeks +/- 5 days (after the first dose of study drug) up to 36 weeks. Thereafter, tumor assessments were performed every 12 weeks +/- 5 days until progressive disease was documented. An independent DMC was instituted for this study to evaluate the safety and efficacy data during the conduct of the study.
Indication/ Main Inclusion Criteria:	Indication: Chemonaïve advanced NSCLC with non-squamous cell histology Inclusion Criteria: Subjects of ≥18 years of age with NSCLC fulfilling the following criteria: • Stage IIIB (with cytologically confirmed malignant pleural or pericardial effusion) or Stage IV histological or cytological confirmation of NSCLC of non-squamous cell carcinoma subtype (amended). • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. • Treatment with gemcitabine and cisplatin considered medically acceptable. • Measurable disease - by CT scan or magnetic resonance imaging (MRI) assessment according to RECIST. • No prior systemic anticancer therapy. • Life expectancy of at least 12 weeks. • Adequate bone marrow, liver, and renal function as assessed by clinical laboratory tests.
Study Objectives:	Overall: The objectives were to compare the efficacy and safety of sorafenib in combination with gemcitabine and cisplatin versus placebo with gemcitabine and cisplatin for the first-line treatment of subjects with Stage IIIB (with effusion) or Stage IV NSCLC.

	Primary: The primary efficacy objective was to compare OS in NSCLC subjects with non-squamous cell carcinoma histology treated with gemcitabine, cisplatin, and sorafenib to subjects treated with gemcitabine, cisplatin, and placebo. Secondary: The secondary efficacy objectives included PFS, tumor responses, and subject reported outcomes (PRO). Evaluation of biomarkers considered as possibly related to the pharmacological mechanism of action of sorafenib with respect to its antitumor activity were optional for subjects and investigators.
Evaluation Criteria:	Efficacy (Primary): The primary efficacy variable was OS, and the primary efficacy analysis was based on non-squamous cell subjects in the intent-to-treat (ITT) population (non-squamous). OS was defined as the time (days) from randomization to death due to any cause. Efficacy (Secondary): Secondary efficacy variables were: • OS based on squamous and non-squamous cell subjects combined in the ITT population (ITT, all). • OS based on squamous cell subjects in the ITT population. • PFS based on the non-squamous cell subjects in the ITT population. PFS was defined as the time (days) from the date of randomization to the date of first observed disease progression (radiological or clinical, whichever was earlier) or death due to any cause, if death occurred before progression was documented. • Time to progression (TTP) in the non-squamous cell subjects in the ITT population. ITT was defined as the time (days) from date of randomization to date of first observed disease progression (radiological or clinical, whichever was earlier). • Percentage of subjects with different tumor response based on the non-squamous cell in the ITT population. Tumor response (= Best Overall Response) of a subject was defined as the best tumor response (confirmed Complete Response (CR: disappearance of tumor lesions), confirmed Partial Response (PR: a decrease of at least 30% in the sum of tumor lesion sizes), Stable Disease (SD: steady state of disease), or Progressive Disease (PD: an increase in the sum of tumor lesions sizes or new lesions)) observed during trial period assessed according to the RECIST criteria (version 1.0) based on Investigator-assessment. • Disease control (DC) based on the non-squamous cell subjects in the ITT population. DC was defined as the total number of subjects whose best response was not progressive disease (total number of CR + PR + SD). • Duration of response (PR or better) based on the non-squamous cell subjects in the ITT population. It was defined as the time (days) from the first documented objective response of PR or CR, whichever was noted earlier, to disease progression or death (if death occurred before progression was documented). • Duration of SD (only evaluated in subjects failing to achieve a best response of CR or PR) based on the non-squamous cell subjects in the ITT population. Duration of SD was defined as the time (days)

	from randomization to the date that disease progression (radiological or clinical, whichever was earlier) was first documented. • Time to response (TTR) based on the non-squamous cell subjects in the ITT population. TTR (for subjects who achieved a response, CR or PR) was defined as the time from date of randomization to the earliest date that response was first documented. • Functional Assessment of Cancer Treatment-Lung (FACT-L) scores based on the non-squamous cell subjects in the ITT population. The FACT-L measures health-related quality of life (HRQOL). • Lung Cancer Subscale (LCS) score based on the non-squamous cell subjects in the ITT population. LCS is a subscale of FACT-L measuring lung cancer specific symptoms. • Time to symptomatic deterioration (TSD) based on the non-squamous cell subjects in the ITT population. TSD was defined as the time from randomization to the date of symptomatic deterioration (≥3 point decline in the LCS score that is maintained for at least 2 consecutive cycles) or death if death occurs before these 2 consecutive cycles are completed. • Euro Quality of life-5D (EuroQol-5D [EQ-5D]) index scores based on the non-squamous cell subjects in the ITT population. • EQ-5D Visual Analog Scale (VAS) scores based on the non-squamous cell subjects in the ITT population. • Change in ECOG performance status. <u>Safety:</u> Safety was assessed based on results of physical examinations including New York Heart Association (NYHA) classification, complete review of body systems, vital signs, electrocardiogram (ECG) data, weight, laboratory values, and adverse events (AEs) up to 30 days after termination of treatment. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 was used for assessment of toxicity and serious adverse events (SAEs) reporting. Safety analyses were based on the valid for safety (SAF, all) population, i.e., all subjects randomized to treatment who received any study medication, and on SAF (non-squamous) and SAF (squamous) populations.
	<u>Other:</u> Biomarker assessments were optional during the study. All biomarker data collected during the entire study period are presented in this report. The biomarker analyses were designed to measure tumor genetic mutations and protein markers with hypothesized relevance based on the mode of action of sorafenib and literature data. Mutational analyses were to include e.g. *EGFR*, *KRAS* and *BRAF* genes.

Statistical Methods:	Efficacy (Primary): The primary efficacy endpoint was OS and the primary efficacy analysis was based on ITT (non-squamous) population. The two treatment groups (sorafenib and placebo) were compared using a log rank test with an overall alpha of 0.025 (α = 0.025) one-sided stratified by the same stratification factors as randomization: ECOG performance status (0 vs 1) and Stage (IIIB with effusion vs Stage IV). The hazard ratio for OS and 95% confidence interval (CI) were provided. Kaplan-Meier estimates and survival curves were also presented for each treatment group. Efficacy (Secondary): Analysis of OS based on squamous and non-squamous cell subjects combined (ITT, all) population was performed as part of the secondary efficacy analyses. The analysis was done as above but taking into account histology subgroup (non-squamous vs squamous) as an additional stratification factor. The OS for ITT (squamous) population was also summarized using Kaplan-Meier estimates and survival curves, but no statistical testing was performed. Subgroup analyses of OS were performed in the ITT (non-squamous) population for the following variables: sex, age group, race, ECOG, stage, country, baseline metastases, liver metastases, and bone metastases. Summaries for the secondary efficacy endpoints were presented by treatment group for ITT (non-squamous), ITT (squamous) and ITT (all) populations. Statistical testing was performed for ITT (non-squamous) and ITT (all) populations, but not for the ITT (squamous) population. Tumor response and disease progression were evaluated based on Investigator-assessments using RECIST tumor response criteria. As supportive analyses, analyses were repeated using independently-assessed RECIST tumor response criteria in approximately half of the subjects. Summary statistics for the PRO endpoints were presented by treatment group for ITT (non-squamous), ITT (squamous) and ITT (all) populations. Statistical testing was performed for the ITT (non-squamous) population using a two-sided significance level of 0.05 (α =0.05). Treatment effect for the FACT-L, LCS, and the EQ-5D total scores was tested using mixed linear models. The time adjusted AUC and time to symptomatic deterioration (TSD) were performed as secondary analyses. This planned final analysis was based on 554 actual events (deaths) in the ITT (non-squamous) population observed up to and including the data cut-off date of 06 APR 2010. Safety: Descriptive summary tables were presented for all safety parameters by treatment group for the safety populations, SAF (non-squamous), SAF (squamous) and SAF (all). Treatment-emergent AEs (TEAEs), drug-related AEs, and safety laboratory parameters were summarized by treatment group as above and by CTCAE grade.

	Analysis of Biomarkers: Correlative analyses were to be performed between mechanistic biomarkers and antitumor activity variables such as PFS, degree of tumor shrinkage, best response, or OS. All biomarker analyses were exploratory.
Number of Subjects:	Planned: 900 (800 subjects with non-squamous cell histology, another 100 subjects with squamous cell histology were already included, when the restriction to non-squamous cell histology subjects was introduced in the Protocol Amendment no. 6) Analyzed: 904 subjects randomized (ITT, all), 901 treated (SAF, all). Three non-squamous subjects in the placebo + GC group did not receive any study drug, and were not considered valid for the safety analysis. Distribution of subjects as per the different analyses sets is summarized in Table 1. **Table 1: Distribution of subjects as per the analyses sets**

Analysis set	Placebo + GC	Sorafenib + GC	Total
ITT (all)	452	452	904
ITT (non-squamous)	387	385	772
ITT (squamous)	65	67	132
SAF (all)	449	452	901
SAF (non-squamous)	384	385	769
SAF (squamous)	65	67	132

GC – gemcitabine and cisplatin; ITT – intent to treat; SAF – safety analysis set

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Study Results

Results Summary — Subject Disposition and Baseline

Out of 1011 screened NSCLC subjects, 904 subjects were randomized: 452 to the sorafenib + GC group and 452 to the placebo + GC group. A subject disposition for the ITT (nonsquamous), ITT (squamous) and ITT (all) populations is presented in Table 2.

Table 2: Subject disposition

	ITT (non-squamous)		ITT (squamous)		ITT (all)	
	P + GC	S + GC	P + GC	S + GC	P + GC	S + GC
Randomized (ITT)	387 (100%)	385 (100%)	65 (100%)	67 (100%)	452 (100%)	452 (100%)
Not treated *	3 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	0 (0.0%)
Treated (SAF)	384 (99.2%)	385 (100%)	65 (100%)	67 (100%)	449 (99.3%)	452 (100%)
Discontinued double-blind treatment	381 (98.4%)	379 (98.4%)	65 (100%)	67 (100%)	446 (98.7%)	446 (98.7%)
Reasons for discontinuing double blind treatment						
Progression measurement proven	235 (60.7%)	197 (51.2%)	27 (41.5%)	13 (19.4%)	262 (58.0%)	210 (46.5%)
Adverse event	71 (18.3%)	99 (25.7%)	11 (16.9%)	18 (26.9%)	82 (18.1%)	117 (25.9%)
Consent withdrawn	16 (4.1%)	32 (8.3%)	3 (4.6%)	4 (6.0%)	19 (4.2%)	36 (8.0%)
Progression by clinical judgment	24 (6.2%)	18 (4.7%)	2 (3.1%)	3 (4.5%)	26 (5.8%)	21 (4.6%)
Amended protocol criteria	0 (0.0%)	0 (0.0%)	18 (27.7%)	22 (32.8%)	18 (4.0%)	22 (4.9%)
Death	11 (2.8%)	16 (4.2%)	1 (1.5%)	5 (7.5%)	12 (2.7%)	21 (4.6%)
Protocol violation	6 (1.6%)	7 (1.8%)	1 (1.5%)	1 (1.5%)	7 (1.5%)	8 (1.8%)
Non-compliant with study medication	7 (1.8%)	6 (1.6%)	1 (1.5%)	1 (1.5%)	8 (1.8%)	7 (1.5%)
Investigator decision, not protocol driven	5 (1.3%)	4 (1.0%)	0 (0.0%)	0 (0.0%)	5 (1.1%)	4 (0.9%)
Lost to follow-up	1 (0.3%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	2 (0.4%)	0 (0.0%)
Second malignancy	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Reason missing	4 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.5%)	0 (0.0%)
On-going on treatment [b]	3 (0.8%)	6 (1.6%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	6 (1.3%)
Entered post-treatment follow-up	372 (100%)	363 (100%)	63 (100%)	62 (100%)	435 (100%)	425 (100%)
Reasons for discontinuing follow-up						
Death	261 (70.2%)	251 (69.1%)	50 (79.4%)	48 (77.4%)	311 (71.5%)	299 (70.4%)
Lost to follow-up	6 (1.6%)	5 (1.4%)	4 (6.3%)	1 (1.6%)	10 (2.3%)	6 (1.4%)
Reason missing/ follow up ongoing [c]	105 (28.2%)	107 (29.5%)	9 (14.3%)	13 (21.0%)	114 (26.2%)	120 (28.2%)

* Reason for not receiving treatment: AE (1), consent withdrawn (1), reason missing (1, CRF comment field: "Patient withdrawn because of thrombotic event")

[b] As of the data cut off 06 APR 2010

[c] Follow-up ongoing at the time of data cut-off:

ITT (non-squamous): 90 patients in the placebo + GC group and 83 in the sorafenib + GC group; reason missing due to consent withdrawal: 9 patients in the placebo + GC group and 16 in the sorafenib + GC group

ITT (squamous): 7 patients in the placebo + GC group and 9 in the sorafenib + GC group; reason missing due to consent withdrawal: 1 patient in the placebo + GC group and 2 in the sorafenib + GC group

ITT (all): 97 patients in the placebo + GC group and 92 in the sorafenib + GC group; reason missing due to consent withdrawal: 10 patients in the placebo + GC group and 18 in the sorafenib + GC group.

Abbreviations: GC – gemcitabline and cisplatin; ITT – intent to treat; P – placebo; S – sorafenib; SAF – safety analysis set

The treatment groups were comparable for demographics and baseline characteristics. In the ITT (non-squamous) population, most subjects were men (59.2% vs 63.3% in the sorafenib + GC and placebo + GC groups, respectively), less than 65 years old (67.5% vs 73.6%), White (69.0% vs 69.5%), had stage IV disease at randomization (87.8% vs 87.9%), ECOG status of 1 (62.1% vs 63.0%), and were past or present smokers (72.1% vs 74.2%).

Also in the ITT (squamous) population, most subjects were men (83.6% vs 80.0% in the sorafenib + GC and placebo + GC groups, respectively), less than 65 years old (61.2% vs 73.8%), White (83.6% vs 75.0%), had stage IV disease at randomization (85.1% vs 87.7%), ECOG status of 1 (55.2% vs 50.8%), and were past or present smokers (91.0% vs 84.6%).

Consequently, in the ITT (all) population, most subjects were men (62.8% vs 65.7% in the sorafenib + GC and placebo + GC groups, respectively), less than 65 years old (66.6% vs 73.7%), White (71.2% vs 70.4%), had stage IV disease at randomization (87.4% vs 87.8%), ECOG status of 1 (61.1% vs 61.3%), and were past or present smokers (74.9% vs 75.7%).

Results Summary — Efficacy

The efficacy results are summarized for the ITT (non-squamous) population in Table 3.

The primary efficacy variable was OS in non-squamous NSCLC subjects treated with sorafenib in combination with GC compared to placebo in combination with GC. In total, 554 death events in the ITT (non-squamous) population were observed. The median OS was 376 days in the sorafenib + GC and 379 days in the placebo + GC group, with an estimated hazard ratio (risk of death with sorafenib + GC versus placebo + GC) of 0.98 (95% CI 0.83 to 1.16), representing a 2% decrease in hazard with sorafenib + GC versus placebo + GC. This did not represent a strong trend favoring either treatment group. The result of stratified log-rank test was not statistically significant showing one-sided p-value of 0.401. The result was not clinically relevant either, compared to the clinically meaningful improvement defined in the protocol as 30% increase in median OS (that is, an estimated hazard ratio of 0.76923, sorafenib over placebo). Based on these results, the study did not meet its primary endpoint.

Subgroup analyses of OS were performed as secondary analyses in the ITT (non-squamous) population. The results showed trends favoring sorafenib + GC treatment for subjects with sex: female (estimated hazard ratio 0.84), race: Asian (0.89), ECOG at randomization: 0 (0.94), country: Germany (0.90) or France (0.92), baseline metastases: <3 (0.90), liver metastases: yes (0.68) and bone metastases: yes (0.75). All 95% CIs for subgroup hazard ratio included 1.0.

The OS analysis in the Chinese ITT (non-squamous) subpopulation showed an estimated hazard ratio of 0.87 (95% CI: 0.58 to 1.30), representing a 13% decrease in hazard with sorafenib + GC versus placebo+ GC. The median OS was 518 and 472 days, respectively. The result was not statistically significant (p=0.244).

OS analyses in the ITT (all) and ITT (squamous) population did not show any clinical benefit for sorafenib + GC treatment. The estimated hazard ratio in the ITT (all) subjects was 1.01 (95% CI: 0.87 to 1.18), representing a 1% increase in hazard with sorafenib + GC vs placebo + GC. This did not represent a strong trend favouring either treatment group. The estimated hazard ratio in subjects with squamous cell histology was 1.22 (95% CI: 0.82, 1.80), representing a 22% increase in hazard with sorafenib + GC versus placebo+ GC. This represented a trend favouring the placebo group.

Table 3: Efficacy results in the ITT (non-squamous) population

ITT (non-squamous)		Placebo + GC	Sorafenib + GC	
		N = 387	N = 385	HR (95% CI)
Median OS, days (95% CI)		379 (335, 414)	376 (333, 416)	0.98 (0.83, 1.16)
Median PFS, days (95% CI)		168 (156, 174)	183 (168, 208)	0.83 (0.71, 0.97)
Median TTP, days (95% CI)		167 (156, 173)	185 (171, 210)	0.73 (0.60, 0.88)
Chinese subpopulation		N = 92	N = 93	
Median OS, days (95% CI)		472 (398, 674)	518 (449, 1006)	0.87 (0.58 to 1.30)
Median PFS, days (95% CI)		163 (131, 175)	215 (169, 251)	0.62 (0.45, 0.85)
		N = 387	N = 385	
ORR (CR + PR), n (%)		100 (26%)	107 (28%)	p=0.27
DCR (CR + PR + SD), n (%)		244 (63%)	239 (62%)	p=0.39
		N = 100	N = 107	
Median duration of response, days (95% CI)		133 (126, 146)	171 (147, 203)	
Median time to response, days		43 (42, 44)	42 (41, 44)	
		N = 210	N = 174	
Median duration of SD, days (95% CI)		131 (125, 156)	144 (126, 168)	
ECOG PS change from baseline		N = 317	N = 297	
No change		175 (55.2%)	172 (57.9%)	
PRO LS means (95% CI)				
FACT-L total score	Cycle 2	94.0 (92.2, 95.9)	90.6 (88.5, 92.6)	
	Cycle 6	93.1 (91.1, 95.1)	89.7 (87.5, 91.8)	
LCS	Cycle 2	20.5 (20.1, 20.8)	19.9 (19.5, 20.4)	
	Cycle 6	20.2 (19.7, 20.6)	19.7 (19.2, 20.1)	
EQ – 5D index	Cycle 2	0.75 (0.73, 0.78)	0.70 (0.67, 0.72)	
	Cycle 6	0.73 (0.70, 0.75)	0.67 (0.64, 0.70)	
EQ – 5D VAS	Cycle 2	68.96 (67.19, 70.72)	66.43 (64.68, 68.18)	
	Cycle 6	68.95 (67.02, 70.87)	66.42 (64.55, 68.30)	

Abbreviations: CI – confidence interval; CR – complete response; DCR – disease control rate; ECOG – Eastern Cooperative Oncology Group; EQ – Euro quality of life; GC – gemcitabine and cisplatin; HR – hazard ratio; ITT – intent to treat; OS – overall survival; ORR – overall response rate; PFS – progression free survival; PR – partial response; PRO – patient reported outcome; PS – performance status; SD – stable disease: TTP – time to progression; VAS – visual analog scale

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In the secondary variable analyses based on investigators' assessments, there was a statistically significant improvement in PFS and prolongation of TTP. In the ITT (non-squamous) population, the median PFS was 183 days in the sorafenib + GC group and 168 days in the placebo + GC group, with estimated hazard ratio of 0.83, representing a 17% decrease in hazard with sorafenib + GC (one-sided p=0.008). The TTP based on investigators' assessments was 185 days in the sorafenib + GC group and 167 days in the placebo + GC group, with estimated hazard ratio 0.73, representing a 27% decrease in hazard with sorafenib + GC (one-sided p=0.0004). However, no statistically significant differences between the sorafenib + GC and placebo + GC treatments were observed in the PFS and TTP analyses based on the independent radiological assessments.

The positive effect of sorafenib + GC treatment to PFS was also seen in the Chinese ITT (non-squamous) subpopulation. The median PFS for the treatment groups was 215 and 163 days, respectively. The estimated hazard ratio was favorable for sorafenib: 0.62 (95% CI: 0.45, 0.85), representing a 38% decrease in hazard with sorafenib + GC versus placebo + GC. The PFS analysis using independent radiological assessments by RECIST was supportive, resulting in an estimated hazard ratio of 0.62 (95% CI: 0.34, 1.11).

Median PFS in the whole ITT (all) population was 182 days for subjects randomized to the sorafenib + GC group and 168 days for subjects randomized to the placebo + GC group. The estimated hazard ratio in all subjects was 0.84, representing a 16% decrease in hazard with sorafenib + GC versus placebo + GC. The result was statistically significant (p=0.008). However, a PFS analysis based on independent radiological assessments did not support this result. Based on the investigator's assessments, the median TTP was 185 days in the sorafenib + GC group and 167 days in the placebo + GC group. The estimated hazard ratio in all subjects was 0.73, representing a 27% decrease in hazard with sorafenib + GC versus placebo + GC. The stratified log-rank test had a statistically significant one-sided p-value of 0.0003. There was an 8% decrease in the hazard with sorafenib + GC vs placebo + GC in the TTP analysis of independent radiological assessments (216 events in total). The result was not statistically significant.

The median PFS in the ITT (squamous) population was 167 days in the sorafenib + GC group and 168 days in the placebo + GC group, and the median TTP was 188 and 160 days, respectively. Analysis of PFS and TTP in the ITT (squamous) population showed an estimated hazard ratio of 0.90 (95% CI: 0.60 to 1.33) for PFS and 0.77 (95% CI: 0.43 to 1.39) for TTP. However, it is difficult to draw conclusions because the Kaplan-Meier curves for the two treatment groups crossed.

The overall response rate (ORR) and DCR of the non-squamous subjects were similar between the treatment groups: ORR was 28% in the sorafenib + GC versus 26% in the placebo + GC group (p=0.27) and DCR 62% vs 63%, respectively (p=0.39). The median duration of response was longer in the sorafenib + GC group compared to the placebo + GC group: 171 days vs 133 days, respectively. Also the median duration of SD was slightly longer with sorafenib + GC: 144 days vs 131 days in the placebo + GC. For more than half of the subjects in both treatment groups (ITT, non-squamous), there was no change in the ECOG performance status.

The PRO endpoints of HRQOL, lung cancer symptom, and general health status as measured by the FACT-L, its subscales LCS and EQ-5D, were similar between the treatment groups at baseline in the ITT (non-squamous) population. The treatment effect was statistically significant in favor of placebo in the mixed linear model and AUC analysis conducted; however, the difference was small and not clinically meaningful. The sorafenib + GC group had longer median time to symptomatic deterioration of 6.9 months (95% CI: 5.8, 8.7) compared to the placebo + GC group of 4.5 months (95% CI: 3.6, 5.9), but it was not statistically significant (p=0.168).

Results Summary — Safety

Exposure to sorafenib/placebo was comparable between the two treatment groups in the SAF (non-squamous) population with median treatment duration of 17 weeks in sorafenib + GC and 18 weeks in placebo + GC group. The median duration in the SAF (squamous) population was 6.6 and 13.0 weeks, respectively.

The overall incidence of TEAEs was comparable in sorafenib + GC vs placebo + GC groups. At least one TEAE was reported for most subjects in the SAF (non-squamous) population during the whole study: 384 (100%) subjects in the sorafenib + GC group and 379 (99%) subjects in the placebo + GC group. In the SAF (squamous) population, at least one TEAE was reported for 67 (100%) and 64 (98%) subjects, respectively. There were more sorafenib/placebo-related TEAEs in subjects treated with sorafenib + GC than placebo + GC. In the SAF (non-squamous) population, sorafenib/placebo-related TEAEs were reported for 331 (86%) subjects in the sorafenib + GC group and 266 (69%) subjects in the placebo + GC group and in the SAF (squamous) population, for 49 (73%) and 44 (68%) subjects, respectively.

In the SAF (non-squamous) population, SAEs were more commonly reported in the sorafenib + GC group: 224 (58%) vs 166 (43%) subjects in the placebo + GC group. Also

treatment-related SAEs were more common in the sorafenib + GC group than in the placebo + GC group: sorafenib/placebo-related: 22% vs 12%; gemcitabine-related: 29% vs 17%; and cisplatin-related: 31% vs 18%. A similar trend was seen in the SAF (squamous) population: Treatment-emergent SAEs were reported for 44 (66%) and 26 (40%) subjects, respectively, and of these sorafenib/placebo-related SAEs for 16% vs 12%; gemcitabine-related 28% vs 18%; and cisplatin-related 31% vs 18% of the subjects, respectively.

Overall, most AEs were of grade 1 or 2. However, most subjects experienced grade 3 to 5 AEs: 92.0% of subjects in the sorafenib + GC group and 80.6% of subjects in the placebo + GC group (SAF, all). In the SAF (non-squamous) population, grade 3 AEs were reported at similar incidence in both groups: 41% in sorafenib + GC and 40% in placebo + GC. The incidence of grade 4 AEs was 38% vs 32%, respectively. In the SAF (squamous) population, grade 3 AEs were reported at higher rate in the sorafenib + GC group: 40% vs 32% in the placebo + GC. The incidence of grade 4 AEs was 30% vs 35%, respectively. In the SAF (squamous) population, the difference in the rate of grade 5 AEs between the treatment groups (sorafenib + GC vs placebo + GC) was greater (21% vs 8%) than in the SAF (non-squamous) population (14% vs 10%).

Deaths were reported at similar incidence in both groups during the study: 71% vs 72%, respectively, in the SAF (non-squamous) population. More deaths were reported in the SAF (squamous) population with similar incidence in both groups: 82% vs 80%, respectively. However, it needs to be taken into account that the cut-off date for enrolling squamous subjects took place earlier (FEB 2008, Amendment 6) than for the non-squamous subjects (FEB 2009) leading to longer disease duration in the SAF (squamous) population. In the SAF (non-squamous) population, deaths within 30 days of study medication were reported in 13% in the sorafenib + GC group and 10% in the placebo + GC group. There was a greater difference between the treatment groups in the SAF (squamous) population: 18% vs 8%, respectively.

The incidence of TEAEs slightly decreased from Chemotherapy to Maintenance phase in both treatment groups: from 100% to 85% in the sorafenib + GC group and from 99% to 72% in the placebo + GC group (SAF, all). In addition, the AEs were milder during the Maintenance phase in both arms. Grade 3 to 5 AEs were reported in 90.5% of subjects in the sorafenib + GC group and 78.2% of subjects in the placebo + GC group during the Chemotherapy phase and in 38.3% and 24.3% subjects, respectively, during the Maintenance phase (SAF, all). A similar trend was seen in the SAF (non-squamous) and SAF (squamous) populations.

During the whole study, the most common TEAEs (in at least 5% of subjects in either treatment arm) by CTCAE category, with similar incidences in both treatment groups in the SAF (all) population were gastrointestinal events (87.6% in sorafenib + GC vs 85.5% in placebo + GC), blood/bone marrow events (78.3% vs 76.4%), constitutional symptoms (66.6% vs 66.1%), pain events (58.0% vs 54.8%), metabolic/laboratory events (45.6% vs 40.8%), pulmonary/upper respiratory events (43.1% vs 42.3%), neurological events (37.6% in both groups), vascular events (14.6% vs 15.6%), renal/genitourinary events (6.6% vs 5.8%), and musculoskeletal/soft tissue events (6.4% vs 6.5%). Dermatology/skin events were reported more frequently in the sorafenib + GC group (64.2% vs 40.8%). Also the incidences of infections (37.6% vs 29.0%), hemorrhage/bleeding events (30.3% vs 21.4%), cardiac general events (24.3% vs 13.6%), cardiac arrhythmias (10.4% vs 8.2%), and allergy/immunological events (6.2% vs 3.6%) were higher in the sorafenib + GC group compared to the placebo + GC group. Auditory/hearing events (8.4% vs 12.0%) and lymphatics (7.3% vs 11.6%) were more common in the placebo + GC group.

The most common TEAEs in SAF (non-squamous) subjects were reported in CTCAE categories gastrointestinal events (88.8% in sorafenib + GC vs 85.9% in placebo + GC), followed by blood/bone marrow events (79.5% vs 77.1%), constitutional symptoms (68.1% vs 65.4%), and pain events (59.5% vs 53.9%). These incidences were comparable between the treatment groups, while dermatology/skin events were reported more commonly in the

sorafenib + GC group (67.8% vs 40.6%). Also the incidences of cardiac general events (25.5% vs 14.1%), hemorrhage/bleeding events (30.9% vs 20.3%), and infections (37.4% vs 29.2%) were higher in the sorafenib + GC group compared to the placebo + GC group. In the SAF (squamous) population, dermatology/skin events were reported with similar incidence in both treatment groups (43.3% vs 41.5%, respectively). On the other hand, in the SAF (squamous) population, higher incidences were reported in the sorafenib + GC group for metabolic/laboratory events (49.3% vs 41.5%), cardiac arrhythmia events (17.9% vs 9.2%), cardiac general events (17.9% vs 10.8%), and renal/genitourinary events (7.5% vs 3.1%).

Blood/bone marrow events, constitutional syndromes, and gastrointestinal events were typical for the Chemotherapy phase. A notable decrease was seen in their incidence from Chemotherapy to the Maintenance phase (blood bone marrow events: from 77.7% to 24.4% subjects in sorafenib + GC and from 75.7% to 13.7% subjects in placebo + GC; constitutional syndromes from 64.8% to 17.2% in sorafenib + GC and from 65.0% to 15.5% in placebo + GC; gastrointestinal events from 87.2% to 37.3% in sorafenib + GC and from 85.1% to 15.5% in placebo + GC). Also dermatology/skin events were less common during the Maintenance phase (27.3% in sorafenib + GC and 10.6% in placebo + GC) than during the Chemotherapy phase (61.7% and 37.9%, respectively).

Comparison of the overall incidences of the most common TEAEs in the SAF (all) population (during the whole study) between the groups by CTCAE (v. 3.0) term revealed similar incidences for AEs in neutrophils (48.2% vs 51.2%), hemoglobin (49.1% vs 50.6%), leukocytes (36.5% vs 33.2%), fatigue (54.4% vs 53.0%), nausea (58.8% vs 55.2%), vomiting (44.7% vs 44.5%), anorexia (39.8% vs 35.2%), constipation (32.7% vs 29.8%), dyspnea (23.9% vs 21.6%), cough (17.9% vs 24.1%), sensory neuropathy (15.7% vs 17.1%), fever (16.6% vs 14.0%), and pain chest/thorax NOS (12.4% vs 14.3%), suggesting that although common, these events were attributable mainly to the underlying disease NSCLC and GC chemotherapy.

The biggest differences between the sorafenib + GC vs placebo + GC groups in the SAF (all) population were observed for the incidence of the following TEAEs: low platelet counts (61.1% vs 48.1%), diarrhea (42.9% vs 18.3%), rash/desquamation (36.9% vs 20.7%), alopecia (32.7% vs 16.5%), hand-foot skin reaction (27.0% vs 3.1%), mucositis (functional/symptomatic), oral (25.4% vs 11.1%), hemorrhage pulmonary, nose (17.5% vs 7.8%), hypertension (17.3% vs 7.6%), hypokalemia (17.0% vs 9.8%), weight loss (12.4% vs 6.9%), hypocalcemia (11.5% vs 4.7%), hypophosphatemia (7.5% vs 2.7%), pruritus (7.7% vs 4.2%), dry skin (7.1% vs 3.3%), infection with normal absolute neutrophil count (ANC), lung (pneumonia) (7.1% vs 4.0%), dysphagia (6.4% vs 1.8%), dermatology - other (specify) (5.5% vs 1.3%), and aspartate transaminase (AST) (5.5% vs 2.7%).

In the SAF (non-squamous) population, the following TEAEs were more common in the sorafenib + GC group compared to the placebo + GC group: low platelet counts (61.8% vs 47.1%), diarrhea (45.2% vs 19.5%), rash/desquamation (37.9% vs 19.8%), alopecia (34.0% vs 17.2%), hand-foot skin reaction (29.1% vs 3.4%), mucositis (functional/symptomatic), oral (26.8% vs 11.5%), hemorrhage pulmonary, nose (18.7% vs 7.6%), hypertension (17.9% vs 7.8%), hypokalemia (18.4% vs 9.4%), and hypocalcemia (12.2% vs 5.2%).

In the SAF (squamous) population, the following TEAEs were more common in the sorafenib + GC group compared to the placebo + GC group: diarrhea (29.9% vs 10.8%), alopecia (25.4% vs 12.3%), mucositis (functional/symptomatic), oral (17.9% vs 9.2%), weight loss (16.4% vs 4.6%), hand-foot skin reaction (14.9% vs 1.5%), hypertension (13.4% vs 6.2%), dysphagia (11.9% vs 1.5%), and infection with normal ANC, lung (pneumonia) (10.4% vs 4.6%).

In the SAF (non-squamous) population, the most common grade 3 to 5 AEs in the sorafenib + GC were low platelets (46.2% vs 25.8% in the placebo + GC), low neutrophils (36.1% vs 37.8%), low leukocytes (23.1% vs 16.7%), low hemoglobin (17.7% vs 10.4%), fatigue (13.0% vs 8.6%) and vomiting (11.9% vs 8.9%). The most common grade 3 to 5 AEs in the SAF (squamous) population were: infection with normal ANC, lung (pneumonia) (9.0% vs 3.1%), supraventricular arrhythmia, atrial fibrillation (6.0% vs 0%), hyperglycemia (6.0% vs 1.5%), constitutional syndromes – other (specify) (4.5% vs 0%), dysphagia (4.5% vs 0%), and hypophsphatemia (4.5% vs 0%).

In the SAF (non-squamous) population, the most common sorafenib/placebo-related AEs (≥5%) by CTCAE category which had clearly higher incidence in the sorafenib + GC group were dermatology/skin events (59.0% vs 26.6%), gastrointestinal events (51.7% vs 39.3%), constitutional syndromes (31.9% vs 26.6%), general cardiac events (16.1% vs 7.6%), pain (15.3% vs 8.6%), metabolic/laboratory events (14.5% vs 9.4%) and hemorrhage/bleeding events (14.3% vs 5.7%). The most common sorafenib/placebo-related AEs by CTCAE term which had higher incidence in the sorafenib + GC group included: rash/desquamation (33.5% vs 15.1%), diarrhea (31.4% vs 10.9%), hand-foot skin reaction (28.8% vs 3.1%), hypertension (14.5% vs 6.3%), mucositis (functional/symptomatic), oral cavity (14.5% vs 5.2%), alopecia (11.2% vs 5.7%), and hemorrhage pulmonary, nose (10.9% vs 2.9%). In the SAF (squamous) population these included: rash/desquamation (28.4% vs 20.0%), diarrhea (17.9% vs 1.5%), hand-foot skin reaction (14.9% vs 1.5%), and platelets (14.9% vs 9.2%).

Analysis of hemorrhage bleeding events revealed some differences between the two histological populations: While in the non-squamous subjects hemorrhage/bleeding events were more commonly reported in the sorafenib + GC group than in the placebo + GC group (30.9% vs 20.3%), in the squamous subjects the incidences were similar in the treatment groups (26.9% vs 27.7%). However, fatal (grade 5) events were reported at higher rate in the squamous subjects (6.0% in sorafenib + GC vs 1.5% in placebo + GC) than in the non-squamous subjects (2.3% vs 0.5%).

Cardiac general events (24.3% vs 13.6%, SAF [all]) including hypertension (17.3% vs 7.6%, SAF, [all]) were overall more common in the sorafenib + GC-treated subjects than in the placebo + GC subjects, regardless of histology. Cardiac ischemia/infarction was reported at similar rates in both groups (2.2% vs 2.4%, SAF, all). Cardiac arrhythmias occurred at higher rates in the sorafenib + GC-treated squamous subjects (17.9% vs 9.2% in the placebo + GC-treated subjects) than in the non-squamous subjects, in whom the incidences were similar between the treatment groups (9.1% vs 8.1%).

Treatment-emergent AEs leading to death (grade 5) were more common in the sorafenib + GC group than in the placebo + GC group: 52 (13.5%) and 39 (10.2%) subjects, respectively, in the SAF (non-squamous) population. The difference was greater in the SAF (squamous) population: AEs leading to death occurred in 14 (20.9%) subjects in the sorafenib + GC group and in 5 (7.7%) subjects in the placebo + GC group. The most common AE reported as death was "death not associated with CTCAE term, disease progression NOS" occurring in 16 (4.2%) vs 9 (2.3%) subjects, respectively, in the SAF (non-squamous) population and in 3 (4.5%) vs 1 (1.5%) subjects, respectively, in the SAF (squamous) population. Fatal grade 5 hemorrhage/bleeding events were reported in 9 (2.3%) subjects in the sorafenib + GC group and in 2 (0.5%) subjects in the placebo + GC group in the SAF (non-squamous) population, and in 4 (6.0%) and 1 (1.5%) in the SAF (squamous) population, respectively. Fatal hemorrhage/bleeding events occurred most commonly in the lung: fatal pulmonary hemorrhage (lung) occurred in 4 (1.0%) subjects in the sorafenib + GC group vs 0% in the placebo + GC group, and pulmonary hemorrhage (broncho pulmonary NOS) in 2 (0.5%) and 1 (0.3%) subjects, respectively, in the SAF (non-squamous) population. In the SAF (squamous) population, fatal pulmonary hemorrhage (lung), pulmonary hemorrhage (broncho pulmonary NOS), and hemorrhage pulmonary, respiratory tract NOS were reported for 1 (1.5%) subject each in the sorafenib + GC group and for none

in the placebo + GC group. Also fatal infections were more common in the sorafenib + GC group with the highest occurrence in the lung: 3 vs 0 subjects (sorafenib + GC vs placebo + GC) in the SAF (non-squamous) population and in 1 subject in the sorafenib + GC group in the SAF (squamous) population.

In general, more SAEs were reported in the sorafenib + GC group compared to the placebo + GC group: 59.3% vs 42.8% in the SAF (all) and 58.2% vs 43.2%, respectively, in the SAE (non-squamous) population. The trend was similar in the SAF (squamous) population (65.7% vs 40.0%). Most SAEs were not related to sorafenib/placebo treatment.

The most common treatment-emergent SAEs by CTCAE category (in at least 5% of subjects in either treatment arm) with higher incidence in the sorafenib + GC group in the SAF (all) population were (sorafenib + GC vs placebo + GC group): blood/bone marrow events (19.2% vs 9.6%), infections (13.3% vs 6.5%), gastrointestinal events (9.3% vs 6.0%), constitutional symptoms (7.5% vs 2.9%), hemorrhage/bleeding events (5.5% vs 2.4%), and pain (5.3% vs 2.9%). Similar incidences of vascular (8.0% vs 7.8%), pulmonary/upper respiratory (7.5% vs 8.2%), and cardiac general (5.1% vs 4.2%) events were reported in both treatment groups.

The most common treatment-emergent SAEs by CTCAE term with higher incidence in the sorafenib + GC group in the SAF (all) population were low platelets (13.9% vs 6.0%), infection with normal ANC, lung (pneumonia) (4.9% vs 2.4%), death not associated with CTCAE term, disease progression NOS (4.2% vs 2.2%), neutrophils (4.2% vs 2.7%), hemoglobin (4.0% vs 2.7%), nausea (3.1% vs 1.3%), and fever (3.1% vs 1.3%). Similar incidences were reported for thrombosis/thrombus/embolism (5.8% vs 4.9%) and dyspnea (4.9% vs 5.8%).

The most common treatment-emergent SAEs with higher incidence in the sorafenib + GC group in the SAF (non-squamous) population were (sorafenib + GC vs placebo + GC group): low platelets: 13.5% vs 5.7%, infection with normal ANC, lung (pneumonia) (4.2% vs 2.3%), death not associated with CTCAE term, disease progression NOS (4.2% vs 2.3%), hemoglobin (4.2% vs 2.6%), neutrophils (3.9% vs 2.1%), nausea (3.4% vs 1.3%), fever (3.1% vs 1.6%), and various hemorrhage/bleeding events (5.2% vs 2.1%). The most common treatment-emergent SAEs with clearly higher incidence in the sorafenib + GC group in the SAF (squamous) population were: infection with normal ANC, lung (pneumonia) (9.0% vs 3.1%), low platelets (16.4% vs 7.7%), supraventricular arrhythmia, atrial fibrillation (6.0% vs 0.0%), various hemorrhage/bleeding events (7.5% vs 4.6%), various metabolic/laboratory events (7.5% vs 3.1%), and various pain events (7.5% vs 3.1%).

Overall, a minority of the subjects in the SAF (all) populations discontinued study medication (sorafenib/placebo, gemcitabine or cisplatin) permanently because of sorafenib/placebo related AEs: 69 (15.3%) subjects in the sorafenib + GC group and 41 (9.1%) subjects in the placebo + GC group. In the SAF (non-squamous) population, the most common sorafenib/placebo-related AEs leading to discontinuation were dermatology/skin events 15 (3.9%) subjects in the sorafenib + GC group and none in the placebo + GC group. Of these, the most common were rash/desquamation (1.6% vs 0%) and hand-foot skin reaction (1.6% vs 0%). Sorafenib/placebo-related vascular events were the next most common reasons: 14 (3.6%) and 16 (4.2%) subjects, respectively. Of these, the most common AE was thrombosis/thrombus/ embolism in 10 (2.6%) vs 12 (3.1%) subjects, respectively. In the SAF (squamous) population, the most common sorafenib/placebo-related AE leading to discontinuation were gastrointestinal events in 2 (3.0%) vs 1 (1.5%) subjects in the sorafenib + GC and placebo + GC groups, respectively. Dermatology/skin events were the most common sorafenib/placebo-related AEs leading to dose reductions in the SAF (non-squamous) (19.7% vs 0.8%) and SAF (squamous) (7.5% vs 0%) populations. Dose interruptions were most commonly due to sorafenib/placebo-related dermatology/skin events (17.1% vs 2.1%) in the SAF (non-squamous) population and blood/bone marrow events (29.9% vs 30.8%) in the SAF (squamous) population.

Around 10% more chemotherapy dose reductions were observed in the sorafenib + GC group compared to the placebo + GC group. However, the mean and median daily doses, treatment durations, and number of dose reductions for gemcitabine and cisplatin were comparable between both treatment groups. An increased incidence of grade 3 and 4 thrombocytopenia in the sorafenib + GC group appeared to be the leading reason for this observed difference in dose reduction rates between the treatment groups.

In the laboratory analyses, grade 3 platelet abnormalities were more common in the sorafenib + GC group than in the placebo + GC group (33% vs 18%) in the SAF (non-squamous) population. The same was seen in the grade 4 platelet abnormalities (24% vs 11%). In the SAF (squamous) population this difference was not seen. Of grade 3 laboratory abnormalities, lymphopenia was more common in the sorafenib + GC group (18% vs 9% in the placebo + GC group) in the SAF (non-squamous) and SAF (squamous) populations (27% vs 9%).

Of grade 3 biochemical laboratory abnormalities, hypophosphatemia was the most common in the SAF (non-squamous) population, detected more frequently in the sorafenib + GC group: 36% vs 9% in the placebo + GC group. Similar trend was seen in the SAF (squamous) population (35% vs 3%).

Results Summary — Other

Analysis of biomarkers:

The overall objective of the biomarker analysis was to determine, if *EGFR*, *KRAS*, or *BRAF* gene mutation, or *EGFR* gene amplification, influenced response of NSCLC patients to sorafenib treatment. *BRAF* mutations were detected at low frequency, and were not analyzed further.

In the overall study population as well as in the subset of patients evaluated for *EGFR* or *KRAS* gene mutation, or *EGFR* gene amplification, no meaningful benefit was derived from sorafenib treatment compared to placebo.

The biomarker analysis showed that:

- *EGFR* gene status (i.e. *EGFR*-mutant) was a positive prognostic factor for OS;
- *EGFR* gene status (mutant or wild type) was not predictive for sorafenib response;
- *KRAS*-mutant gene status was a negative prognostic factor for OS;
- *KRAS* gene status (mutant or wild type) was not predictive for response to sorafenib;
- *EGFR* gene amplification did not appear to be prognostic, but may be predictive for sorafenib response, but the sample size in this study was insufficient for this to be conclusive..

Conclusion(s)

This study did not meet its primary endpoint of improved OS when sorafenib was added to a regimen of GC in subjects with advanced, non-squamous NSCLC. In the secondary endpoint analyses, there was a statistically significant improvement of the PFS and prolongation of TTP when sorafenib was added to the GC chemotherapy. The observed inferior overall survival for squamous subjects treated with GC plus sorafenib compared to those treated with GC plus placebo cannot be assigned to an identifiable single safety finding. AEs were as expected; no new toxicities were observed.

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Marketing Authorization Holder in Germany	
Name	Bayer Pharma AG
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Sponsor in Germany	
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37	Nouvel Hopital CIVIL-CHU Strasbourg	Hôpital de Jour UF 2099 Pneumologie Pole de Pathologie Thoracique 1 place de l'hôpital BP426	67901	Strasbourg	FRANCE
38	Asklepios Fachkliniken München Gauting	Zentrum für Pneumologie und Thoraxchirurgie Robert-Koch-Allee 2	82131	Gauting	GERMANY
39	Asklepios Klinik Harburg	Lungen und Bronchialheilkunde Eißendorfer Pferdeweg 52	21075	Hamburg	GERMANY
40	Kliniken der Stadt Köln - Städt. Krankenhaus Köln-Merheim	Lungenklinik - Haus 23/24 Ostmerheimer Straße 200	51109	Köln	GERMANY
41	Klinik Löwenstein gGmbH	Medizinische Klinik II Onkolgie Im Geißhölzle 62	74245	Löwenstein	GERMANY
42	Krankenhaus Großhansdorf	Zentrum für Pneumologie und Thoraxchirurgie Onkologischer Schwerpunkt Wöhrendamm 80	22927	Großhansdorf	GERMANY

43	Krankenhaus Hofheim am Taunus	Medizinische Klinik III Pneumologie Lindenstr. 10	65719	Hofheim	GERMANY
44	Städtisches Klinikum "St. Georg" Leipzig	Robert-Koch-Klinik Pneumologie Nikolai-Rumjanzew-Str. 100	04207	Leipzig	GERMANY
45	St. Markus-Krankenhaus	Medizinische Klinik I Wilhelm-Epstein-Str. 2	60431	Frankfurt	GERMANY
46	St. Vincentius-Kliniken gAG	Medizinische Klinik II Hämatologie, Onkologie, Immunologie Südenstr. 32	76137	Karlsruhe	GERMANY
47	Thoraxklinik Heidelberg	Onkologie Amalienstr. 5	69126	Heidelberg	GERMANY
48	Universitätsklinikum Essen	Innere Klinik und Poliklinik Tumorforschung Westdeutsches Tumorzentrum Hufelandstr. 55	45122	Essen	GERMANY
49	Zentralklinik Bad Berka GmbH	Klinik für Pneumologie Robert- Koch-Allee 9	99437	Bad Berka	GERMANY
50	Sotiria General State Hospital of Chest Diseases	Athens University Medical School, Department of Internal Medicine - Oncology 152 Mesogion Ave.	11527	Athens	GREECE
51	University General Hospital of Heraklion	Department of Internal Medicine -Oncology P.O. Box 1352 3rd building - 1st floor	711 10	Heraklion	GREECE

52	Barzilai Medical Center	3, Hahistadrut Street	78278	Ashkelon	ISRAEL
53	Chaim Sheba Medical Center	Tel-Aviv University Tel Hashomer 52621	52621	Tel Hashomer	ISRAEL
54	Edith Wolfson Medical Center	62, Halochamim Street P.O.B. 5	58100	Holon	ISRAEL
55	Kaplan Medical Center	P.O.B. 1	76100	Rehovot	ISRAEL
56	Meir Medical Center	Clalit Health Services 59, Tchernichovsky Street	44281	Kfar Saba	ISRAEL
57	A.O.R.N. Garibaldi	Oncologia Medica P.O. Garibaldi-Nesima Via Palermo 511 (636) 3° Piano, Torre A	95122	Catania	ITALY
58	A.O. San Camillo-Forlanini	Oncologia Medica Circonvallazione Gianicolense, 87	00152	Roma	ITALY
59	A.O. San Gerardo di Monza	Oncologia Medica Via Pergolesi, 33	20052	Monza	ITALY
60	A.O.U. Careggi	Oncologia Medica Viale Pieraccini, 17	50139	Firenze	ITALY
61	A.O.U. di Bologna	Oncologia Medica - Padiglione 2 Dip. Ematologia, Oncologia e Medicina di Laboratorio Policlinico S.Orsola-Malpighi Via Albertoni, 15	40138	Bologna	ITALY

62	A.O.U. Integrata Verona	Oncologia Medica Policlinico G.B. Rossi (Borgo Roma) Piazzale L. Scuro, 10	37134	Verona	ITALY
63	ASL Sassari - Sardegna	Oncologia Medica P.O. SS. Annunziata Via E. de Nicola	07100	Sassari	ITALY
64	AULSS 12 Veneziana - Veneto	Oncologia Medica P.O. SS. Giovanni e Paolo Castello 6777	30122	Venezia	ITALY
65	AUSL 06 Livorno - Toscana	Oncologia Medica P.O. di Livorno Viale Alfieri, 36	57124	Livorno	ITALY
66	IRCCS Centro di Riferimento Oncologico	Oncologia Medica A Via F.Gallini, 2	33081	Aviano	ITALY
67	IRCCS Fondazione San Raffaele	Oncologia Medica Istituto Scientifico Universitario San Raffaele Via Olgettina, 60	20132	Milano	ITALY
68	IRCCS Ist Clinico Humanitas	Oncologia Medica ed Ematologia Via Manzoni, 56	20089	Rozzano	ITALY
69	Antiguo Hospital Civil de Guadalajara "Fray Antonio Alcalde"	Oncology Hospital No. 278 Col. El Retiro Sector Hidalgo	44280	Guadalajara	MEXICO
70	Hospital Universitario "José Eleuterio González"	Servicio de Hematología Av. Madero y Gonzalitos S/N Col Mitras Centro	64460	Monterrey	MEXICO

71	Instituto Nacional de Cancerología	Av. San Fernando N° 22 Col. Sección XVI Delegación Tlalpan	14080	México	MEXICO
72	Atrium Medisch Centrum	Afdeling Longziekten, H.Dunantstraat 5	6419 PC	HEERLEN	NETHERLANDS
73	Jeroen Bosch Ziekenhuis	Tolbrugstraat 11	5211 RW	DEN BOSCH	NETHERLANDS
74	St. Antonius Ziekenhuis	Afdeling Longziekten Koekoekslaan 1	3435 CM	NIEUWEGEIN	NETHERLANDS
75	Ziekenhuis Gelderse Vallei	Afdeling Longziekten, Willy Brandtlaan 10	6716 RP	Ede	NETHERLANDS
76	Ziekenhuis St. Jansdal	St. Jansdal - Longziekten - Weth. Jansenlaan 90	3844 DG	HARDERWIJK	NETHERLANDS
77	Consorci Sanitari de Terrassa	Servicio de Oncología Ctra. de Torrebonica, s/n	08227	Terrassa	SPAIN
78	Hospital Arnau de Vilanova de Valencia	Servicio de Oncología c/ San Clemente, 12	46015	Valencia	SPAIN
79	Hospital Clínico Universitario de Valencia	Servicio de Oncología Avda. Blasco Ibañez, 17	46010	Valencia	SPAIN
80	Hospital de Cruces	Servicio de Oncología Pza. de Cruces, s/n	48903	Cruces/Barakaldo	SPAIN
81	Hospital de la Santa Creu i de Sant Pau	Servicio de Oncología C/Mas Casanovas, 90	08025	Barcelona	SPAIN
82	Hospital General Universitario de Valencia	Servicio de Oncología Avda Tres Cruces, s/n	46014	Valencia	SPAIN

83	Hospital Regional Carlos Haya	Servicio de Oncología Médica Avda. Carlos Haya s/n	29010	Málaga	SPAIN
84	Hospital Universitario 12 de Octubre	Servicio de Oncologia. Ed.Materno Infantil. 2ª planta. Av. de Córdoba, s/n	28041	Madrid	SPAIN
85	Hospital Virgen de la Victoria	Servicio de Oncología Médica C/ Campus Universitario de Teatinos, s/n	29010	Málaga	SPAIN
86	Inselspital Bern	Klinik und Poliklinik für Medizinische Onkologie Freiburger Str. 4	3010	Bern	SWITZERLAND
87	Universitätsspital Basel	Onkologie Petersgraben 4	4031	Basel	SWITZERLAND
88	Aberdeen Royal Infirmary	Ward 17 Anchor Unit Forester Hill	AB25 2ZN	Aberdeen	UNITED KINGDOM
89	Addenbrookes Hospital	Cambridge Cancer Trials Centre Oncology Clinical Trials (S4) Box 279	CB2 0QQ	Cambridge	UNITED KINGDOM
90	Guy's Hospital	St Thomas Street	SE1 9RT	London	UNITED KINGDOM
91	New Cross Hospital	Deanesly Centre Wolverhampton Road Heath Town	WV10 0QP	Wolverhampton	UNITED KINGDOM
92	Royal Marsden Hospital (London)	Department of Medical Oncology 1st Floor Mullberry House Fulham Road	SW3 6JJ	London	UNITED KINGDOM
93	Royal Marsden NHS Trust (Surrey)	Downs Road	SM2 5PT	Sutton	UNITED KINGDOM

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