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:	13266	EudraCT number: 2008-006914-62 NCT00863746
Study Phase:	III	
Official Study Title:	A Phase III, multi-center, placebo-controlled trial of Sorafenib (BAY 43-9006) in patients with relapsed or refractory advanced predominantly non-squamous Non-Small Cell Lung Cancer (NSCLC) after 2 or 3 previous treatment regimens for advanced disease	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Sorafenib (Nexavar, BAY 43-9006)	
Name of Active Ingredient:	4-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic acid methylamide-4-methylbenzenesulfonate	
Dose and Mode of Administration:	400 mg (2 tablets of 200 mg) twice daily (bid), mornings and evenings. Total daily dose 800 mg Oral	
Reference Therapy/Placebo		
Reference Therapy:	Placebo	
Dose and Mode of Administration:	2 tablets bid, mornings and evenings Oral	
Duration of Treatment:	Sorafenib was taken on a continuous basis with each treatment cycle consisting of 21 days and with no interruption between cycles. A patients study treatment was continued until the occurrence of: • Unequivocal evidence of disease progression; • Intolerable toxicity; • Patient's consent was withdrawn. Treatment could be discontinued at the investigator's discretion	
Studied period:	**Date of first subjects' first visit:**	29 APR 2009
	Date of last subjects' last visit:	02 APR 2013 (data cut-off date: 16 MAR 2012)
Premature Study Suspension / Termination:	Not applicable	

Substantial Study Protocol Amendments	**Amendment 1 (16 Jun 2009)** local amendment for Japan centers only to enable investigators to detect the potential risk of interstitial lung disease (ILD) at an early stage by specifying timepoints of radiological assessments. **Amendment 2 (21 May 2009)** local amendment for Japan centers only to reduce the dose of radiation to patients enrolled into the study. **Amendment 3 (16 JUL 2009)** inclusion criteria changed to clarify that patients with a history of metastatic or meningeal tumors were to be asymptomatic and off steroid treatment 14 days before study entry; exclusion of patients with CTCAE grade 2 or 3 bleeding with in 4 weeks of administration of study drug; a change allowing prior investigational anti-cancer regimens if at least one drug was approved for the treatment of NSCLC and if all drugs were stopped at least 4 weeks before first dose of study drug; patients would be removed from study treatment if they required dose reductions below level 2 due to toxicity or due to progression or recurrence of the underlying cancer. **Amendment 4 (16 FEB 2010)** in the inclusion criteria adjuvant or neo-adjuvant anti-cancer treatments after a relapse within 1 year of therapy was counted as a prior treatment regimen. Maintenance anti-cancer treatment was counted as a separate regimen; patients with current chronic active or acute hepatitis B or C and patients with previously untreated or concurrent cancer in a site distinct from the primary site or histology of NSCLC were excluded from the study. Prior anti-cancer drugs for NSCLC were to be completed at least 3 weeks prior to first dose of study drug. The evaluation of urine samples was deleted from the pharmacogenomics biomarker evaluation. A separate consent form for long-term follow-up for patients withdrawing from the treatment was required. An interim analysis for futility only would be performed when approximately 50% of the planned death events for the final analysis were observed. **Amendment 5 (09 NOV 2010)** Text was added stating that the power of the study was increased to 92.6%, and that the number of events (deaths) were increased to 572. Overall survival data were to be considered mature after 572 events estimated to occur after 30 to 32 months. Furthermore, no interim analysis was to be performed, and additional details were given regarding prior treatments that were to be excluded during the study (e.g. VEGF(R) inhibitors). **Protocol amendment 6 (24 MAY 2012)** Ongoing patients receiving sorafenib at the time of overall study unblinding following primary completion could continue if considered beneficial by the principal investigator at the site. Sorafenib was to be administered in accordance with the protocol until the patient could access sorafenib outside the study or no longer benefited from treatment.

Study Center(s):	This multinational study with patients screened in 157 centers across 33 countries in: **Northern and Western Europe** [Italy (9) Spain (9), United Kingdom (8), France (8), Sweden (5), Germany (7), Netherlands (6), Greece (3), Belgium (3), Austria (2), Turkey (5)] Israel (6), and South Africa (3), **Eastern Europe** [(Bulgaria (5), Hungary (6), Poland (5), Russia (5)], **North America** [(United States (2), Canada (1)], **South America** (Brazil (7), Chile (2), Peru (3)], and **Asia-Pacific** [China (12), Hong Kong (2), India (3), Indonesia (1), Japan (8), Pakistan (2), Philippines (4), Republic Of Korea (5), Singapore (2), Taiwan (5), and Thailand (3)].
Methodology:	**Overall Survival (OS):** All randomized patients were followed for survival information. After discontinuation of study drug treatment, patients continued into the post-treatment follow-up period and were contacted every months until death was recorded. Tumor response and disease progression assessments was based on investigator's assessment according to the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.0) tumor response criteria of the chest, abdomen and pelvis. Non-target lesions were also recorded. Radiological assessments (CT/MRI) were performed at screening, and every 6 weeks (after the first dose of study drug). PRO on Health Related Quality of Life (HRQoL), lung cancer symptoms, and health state utilities were using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire for Palliative Care (EORTC QLQ-C15-PAL), the EORTC QLQ-lung cancer module (EORTC QLQ-LC13), and the EuroQol-5D (EQ-5D). An independent Data Monitoring Committee (DMC) was instituted for this study to evaluate the safety and efficacy data during the conduct of the study. However, no formal interim analysis for futility or efficacy was conducted.
Indication/ **Main Inclusion Criteria:**	Advanced predominantly non-squamous NSCLC Patients of ≥18 years of age (≥20 for Japan) with NSCLC fulfilling the following criteria: • Advanced relapsed or refractory predominantly non-squamous NSCLC. The diagnosis was required to have been confirmed cyto-/ histologically; • At least 2 but not more than 3 prior treatment regimens for advanced NSCLC; • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; • Measurable disease, with measurable lesions accurately measurable one-dimensionally as ≥20 mm by computed tomography (CT), positron emission tomography (PET), X-ray, magnetic resonance imaging (MRI), and as ≥10 mm by spiral CT, or non-measurable disease assessed by conventional techniques as <20 mm or <10 mm by spiral CT. Assessments were according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0); • Adequate bone marrow, liver and renal function as assessed by clinical laboratory examinations • Life expectancy of at least 12 weeks

Study Objectives:	The objective of this phase III study was to compare the efficacy and safety of sorafenib monotherapy plus best supportive care (BSC) versus placebo plus BSC for the treatment of patients with relapsed or refractory advanced predominantly non squamous NSCLC after 2 or 3 prior treatment regimens for advanced disease **Primary efficacy objective:** • Overall survival (OS) **Secondary objectives:** • Progression-free-survival (PFS); • Disease control rate (DCR); • Best overall response rate (ORR); • Time to progression (TTP); • Patient reported outcomes (PRO) on Health Related Quality of Life (HRQoL), lung cancer symptoms, and health state utilities; • Safety. **Other objectives:** Evaluation of biomarkers

Evaluation Criteria:	**Efficacy** The primary efficacy variable was OS, and the primary efficacy analysis was based on patients in the Full Analysis Set (FAS) population. OS was defined as the time from randomization to death due to any cause. Secondary efficacy variables were: • PFS, defined as the time from the date of randomization to the date of first observed disease progression (radiological or clinical, whichever occurred earlier) or death due to any cause, if death occurred before progression was documented. • DCR, defined as the proportion of patients whose best response was 'complete response' (CR), 'partial response' (PR), or 'stable disease' (SD) according to RECIST (version 1.0). In case of SD, measurements had to meet the stable disease criteria at least once after study entry at a minimum interval of 6 weeks. • ORR, defined as the proportion of patients whose best response was CR or PR according to RECIST (version 1.0). • TTP, defined as the time from randomization to the first documented disease progression according to the investigator's assessment. Disease progression could be radiological progression or clinical progression. TTP for patients without disease progression or death at the time of analysis were to be censored at the date of the last tumor scan • PRO including HRQOL, lung cancer symptom, and general health status as measured by the EORTC QLQ-C15-PAL, the EORTC QLQ-LC13, and the EQ-5D, respectively. **Safety** Safety was assessed based on results of physical examinations including New York Heart Association (NYHA) classification, assessment of ECOG PS, 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 event (SAE) reporting. Safety analyses were based on the valid for safety (SAF) population, i.e. all patients randomized to treatment who received any study medication.

Statistical Methods:	The primary efficacy endpoint was OS analyzed in the FAS population. The two treatment groups (sorafenib + BSC and placebo + BSC) were compared using a one-sided log-rank test with an overall alpha of 0.025, stratified by the same stratification factors as used for randomization: Number of prior systemic therapies: '2' or '3'; brain metastases: 'yes' or 'no'; prior epidermal growth factor receptor (EGFR) inhibitor treatment: 'yes' or 'no'; geographic Region: 'core region' or 'non-core region' (Core regions: North America, Northern and Western Europe; Non-core regions: South America, Eastern Europe, Asia-Pacific). The hazard ratio for OS and 95% confidence interval calculated by stratified proportional hazards regression using the same stratification factors as for randomization were provided. Kaplan-Meier estimates and survival curves were also presented for each treatment group. The secondary endpoints PFS and TTP were analyzed as described for the primary efficacy endpoint OS. The secondary endpoints DCR and ORR were analyzed using the one-sided Cochran-Mantel-Haenszel test with an alpha of 0.025 adjusted for the same stratification factors as those used at randomization. The estimates of DCR and ORR by treatment as well as the differences of these rates between treatment groups and the corresponding 95% confidence intervals (CIs) were computed. Subgroup analyses of OS, PFS, TTP, and ORR were performed for the following subgroups: Stratification factors (2 versus 3 prior systemic therapies, brain metastases documented – yes/no, with versus without prior EGFR inhibitor treatment, core geographic region [Group 1: North America, Northern and Western Europe] versus non-core geographic region [Group 2: South America, Eastern Europe, Asia-Pacific] and other subgroups (age [<65, ≥65, ≥75 years], sex, baseline ECOG performance status 0 or 1, duration of prior EGFR treatment less than 12 weeks or longer than 12 weeks, prior EGFR treatment with PR or CR as best overall response, East Asian population [China, Hong Kong, Japan, Korea, Taiwan], and Non-East-Asian population). All PRO analyses were performed in the PROAS population, i.e., for all FAS patients who had evaluable PRO assessments at baseline and at least one post-baseline assessment. PRO endpoint were summarized by descriptive statistics and treatment effects were analyzed using a mixed linear model (random coefficient model) and applying a 2-sided type-I error of 0.05. PRO endpoints were analyzed using a two-sided significance level of 0.05. Further analyses were conducted to explore treatment effect on HRQOL and to examine the mechanism underlying missing data, The safety data were summarized using descriptive statistics for the SAF population. The final analysis was based on 579 actual death events in the FAS population observed up to and including the data cut-off date of 16 MAR 2012.
Number of Subjects:	**Planned**: Approximately 700 patients (350 in each arm) **Analyzed:** 703 patients

Study Results

Results Summary — Subject Disposition and Baseline

Out of 1002 screened NSCLC patients, 703 patients were randomized: 350 to the sorafenib + BSC group and 353 to the placebo + BSC group.

The treatment groups were comparable for **demographics and baseline characteristics**. In the FAS population, most were men (53.1% in the sorafenib + BSC group versus 59.2% in the placebo + BSC group), were younger than 65 years-of-age (68.3% versus 62.9%), and the highest proportion of patients were Asian (50.0% versus 49.3%) followed by White (43.7% versus 44.5%), the majority of patients were past or present smokers, 51.7% versus 61.2%.

The majority of patients had at baseline more than one tumor site. The sites of the cancer were widely distributed, predominantly in the lung with 88.0% in the sorafenib + BSC group and 87.3% in the placebo + BSC group, lymph nodes (54.6% versus 48.2%), pleura (32.6% versus 32.0%), bone (26.0% versus 30.0%), and liver (14.6% versus 19.0%).

The majority of patients had an ECOG status of 1, 66.6% in the sorafenib + BSC and 68.6% in the placebo + BSC group, about one third each a status of 0 (31.4% versus 31.2%). Most patients had tumor node metastasis (TNM) stage IV, 61.1% in the sorafenib + BSC group and 63.2% in the placebo + BSC group, and stage IIIB (17.1% versus 15.3%). TNM grading at study entry was stage IV for 95.4% of the patients in the sorafenib + BSC group and for 94.3% in the placebo + BSC group and stage IIIB (4.6% versus 5.4%).

Results Summary — Efficacy

The primary efficacy variable was **OS** in non-squamous NSCLC patients treated with sorafenib in combination with BSC compared to placebo in combination with BSC. In total, 579 (82.4%) death events in the FAS population were observed up to and including the data cut-off date. The median OS was 248 days in the sorafenib + BSC and 253 days in the placebo + BSC group, with a hazard ratio (risk of death with sorafenib + BSC versus placebo+ BSC) of 0.993 (95% CI: 0.841; 1.174) for data stratified as per CRF, representing no relevant decrease in hazard with sorafenib + BSC versus placebo+ BSC. The one-sided stratified log-rank test showed with a p-value of 0.469 for data stratified as per Case Report Form (CRF) no statistically significant difference in treatments on OS. Based on these results, the study did not meet its primary endpoint.

Subgroup analyses of OS were performed in the FAS population. The results indicated no statistically relevant trends favoring sorafenib + BSC treatment; the 95% CIs of all subgroup hazard ratios included unity. The hazard ratios for all subgroups ranged between 0.77 and 1.19 and some decreases were seen for patients within the age group at randomization: ≥75 years (0.77), from the non-core region (Group 2: South America, Eastern Europe, Asia-Pacific) (HR = 0.89), with presence of brain metastases at baseline: yes (0.85), with number of prior treatments: 2 (0.84), and for the East Asian population (0.84).

Based on investigators' assessments using RECIST version 1.0, there was a statistically significant improvement of the **PFS** in the FAS population. The median 84 days of PFS in the sorafenib + BSC group and of 43 days in the placebo + BSC group were based on 294 (84.0%) and 330 (93.5%) events, respectively. The estimated hazard ratio (risk of progression or death before progression with sorafenib + BSC versus placebo+ BSC) was 0.607 (95% CI: 0.514; 0.717) for data stratified as per CRF representing a decrease of about 39% in hazard with sorafenib + BSC versus placebo + BSC. The stratified one-sided log-rank test showed a statistically significant p-value of <0.0001.

Subgroup PFS results showed clear trends favoring sorafenib + BSC for almost all subgroups. Decreases in PFS hazard ratios were between 10% and 55% and corresponding 95% CIs being below unity were observed for almost all patient subgroups, except for the core-region (Group 1: North America, Northern/Western Europe), age groups 65 – 74 years and ≥75 years.

Similarly to PFS, prolongation of median **TTP** was observed in the FAS population. The median TTP based on investigators' assessments was 89 days in the sorafenib + BSC group and 43 days in the placebo + BSC group, based on 243 (69.4%) and 298 (84.4%) events, respectively. The estimated hazard ratio (risk of progression with sorafenib + BSC versus placebo + BSC) was 0.542 (95% CI: 0.453; 0.649) for data stratified as per CRF representing a 46% decrease in hazard with sorafenib + BSC versus placebo + BSC. The stratified one-sided log-rank test had a statistically significant p-value of <0.0001.

Subgroup TTP results showed clear trends favoring sorafenib + BSC for almost all subgroups. Decreases in TTP hazard ratios were between 31% and 56% and corresponding 95% CIs being below unity were observed for almost all patient subgroups, except for the age group ≥75 years.

Regarding the **ORR**, a statistically significant effect and clinical benefit was observed for sorafenib + BSC treatment over placebo + BSC treatment in the analyses. In the FAS population, the overall response rate based on the investigator's assessments was 4.86% (95% CI: 2.85%; 7.66%) for the sorafenib + BSC group and 0.85% (95% CI: 0.18%; 2.46%) for the placebo + BSC group (one-sided p = 0.000876 for CRF based data and p = 0.001001 for Interactive voice response system (IVRS) based data).

The **DCR** in the FAS population was statistically significantly higher in the sorafenib + BSC group compared to the placebo + BSC group based on the investigators' assessments: 47.14% (95% CI: 41.81%; 52.52%) for the sorafenib + BSC group and 24.65% (95% CI: 20.24%, 29.48%) for the placebo + BSC group (one sided p<0.000001, independently from source of stratification data).

The **PRO** endpoints of HRQOL, lung cancer symptom, and health state utilities were measured by the EORTC QLQ-C15-PAL, EORTC QLQ-LC13, and EQ-5D, respectively, and were similar between the treatment groups at baseline. There was no difference in global health status/QoL, physical and emotional functioning between the two treatment groups, as measured by the EORTC QLQ-C15-PAL. More problems with 'alopecia', dysphagia', and 'sore mouth' were seen in the sorafenib + BSC compared with the placebo + BSC group as indicated by EORTC QLQ-LC13. Exploratory analyses, applying a classification into improved, stable or worsened item scales for patients, showed statistically significant differences in emotional functioning (p = 0.004), i.e. more improvements in the sorafenib + BSC group and more stable patients in the placebo + BSC group. A higher fraction of sorafenib + BSC patients in the worsened category were observed for the items 'dysphagia', alopecia', and sore mouth', indicating a relation to treatment with the study drug. For the items 'coughing', 'pain (general)', 'pain in arm or shoulder' and 'pain in chest' the fraction of sorafenib + BSC patients showing improvement was higher compared with the placebo + BSC group. There was no difference in health state utilities or Visual analogue scale (VAS) scores as measured by EQ-5D between the treatments groups.

Results Summary — Safety

The safety conclusions presented in this report reflect data accumulated up to and including the cut-off date of 16 MAR 2012.

Duration of exposure to study drug in the SAF population was not similar between the treatment groups. The median treatment duration was 12.0 weeks in sorafenib + BSC group and 6.3 weeks in placebo + BSC group. The mean actual daily dose in the FAS population for the sorafenib + BSC group was 720.10 mg and 796.07 mg for the placebo + BSC group. By category, 64% of the patients in the sorafenib + BSC group received an actual daily dose of 800 mg and 34.9% of the patients less than 800 mg. In the placebo + BSC group, 92.9% of the patients received an actual daily dose of 800 mg.

The **overall incidence of Treatment-Emergent Adverse Events (TEAEs)** was comparable between the treatment groups. In the SAF population, at least one TEAE was reported for most patients during the whole study: 342 (98.8%) patients in the sorafenib + BSC group and 318 (90.6%) patients in the placebo + BSC group. Treatment-emergent AEs considered to be related to treatment with sorafenib/placebo were more commonly reported in the sorafenib + BSC than in placebo + BSC group, for 304 (87.9%) patients versus 173 (49.3%) patients, respectively.

SAEs were slightly more common in the sorafenib + BSC than in the placebo + BSC group: 135 (39.0%) versus 111(31.6%) patients, respectively. Most SAEs were not related to sorafenib/placebo-treatment based on investigator-assessment. Treatment-related SAEs were slightly more common in the sorafenib + BSC group than in the placebo + BSC group: sorafenib/placebo-related (8.1% versus 3.1%).

There were fewer grade 1 and 2 but more **grade 3** TEAEs in the sorafenib + BSC group compared to the placebo + BSC group; 4.9% versus 19.1% for grade 1, 26.6% versus 32.8% for grade 2, and 40.2% versus 18.8% for grade 3. The incidence of **grade 4** AEs was similar, 4.0% versus 6.8%, respectively.

During the study, the **most common TEAEs by CTCAE category** in the SAF population and reported with higher incidence in the sorafenib + BSC versus the placebo + BSC group were gastrointestinal events (74.0% versus 49.3%), dermatology/skin events (77.2% versus 23.1%), constitutional symptoms (54.0% versus 39.0%), metabolic laboratory events (32.1% versus 13.7%), and general cardiac events (22.3% versus 7.7%). Also the incidences of pain events (57.5% versus 49.9%), infection (25.7% versus 18.8%), hemorrhage/bleeding (16.2% versus

11.1%), blood/bone marrow events (15.6% versus 8.0%), and cardiac arrhythmia events (11.3% versus 5.7%) were slightly higher in the sorafenib + BSC than in the placebo + BSC group.

Common TEAEs by CTCAE category with comparable incidences were pulmonary/upper respiratory events (47.1% versus 43.3%), neurology events (21.1% versus 17.4%), deaths (7.2% versus 4.0%), musculoskeletal/soft tissue events (5.8% versus 6.0%), and ocular/visual events (5.5% versus 1.7%).

The following **TEAEs by CTCAE term** were more common in the sorafenib + BSC group compared to the placebo + BSC group: hand-foot skin reaction (55.2% versus 6.0%), rash/desquamation (40.5% versus 12.3%), fatigue (36.1% versus 27.6%), diarrhea (35.8% versus 12.0%), anorexia (30.3% versus 17.7%), hypertension (19.7% versus 4.6%), alopecia (18.8% versus 1.1%), mucositis (functional/symptomatic) oral cavity (16.8% versus 4.3%), weight loss (12.4% versus 4.8%), fever (11.6% versus 5.4%), pain, abdomen NOS (10.4% versus 4.0%), proteinuria (7.8% versus 1.7%), and hypokalemia (7.2% versus 0.9%).

The **most common grade 3 to 5 TEAEs**, reported at higher incidence in the sorafenib + BSC versus the placebo + BSC group, included hand-foot skin reactions (16.2% versus 0.6%), fatigue (8.7% versus 4.3%), hypertension (5.5% versus 0.6%), and rash/desquamation (4.0% versus 0%). Common but with comparable incidences was death not associated with CTCAE term, disease progression NOS (5.8% versus 3.7%).

The **most common sorafenib/placebo-related TEAEs (≥5%) by CTCAE category** which had clearly a higher incidence in the sorafenib + BSC group were dermatology/skin events (75.1% in the sorafenib + BSC group versus 18.8% in the placebo + BSC group), gastrointestinal events (55.8% versus 24.8%), constitutional symptoms (26.0% versus 14.2%), pain (21.1% versus 5.7%), metabolic/laboratory events (17.9% versus 4.6%), and cardiac general events (17.1% versus 4.0%). Disparate incidences were also seen for hemorrhage/bleeding events (8.4% versus 2.8%) and blood/bone marrow events (7.8% versus 2.3%).

The **most common sorafenib/placebo-related TEAEs by CTCAE term** which had a higher incidence (difference ≥10%) in the sorafenib + BSC group included: hand-foot skin reaction (54.9% versus 6.0%), rash/desquamation (38.2% versus 10.5%), diarrhea (30.1% versus 6.6%), fatigue (21.4% versus 11.7%), anorexia (19.7% versus 6.8%), alopecia (17.6% versus 0.9%), hypertension (16.2% versus 3.4%), and mucositis (functional/symptomatic) oral cavity (13.9% versus 3.1%).

The **most common treatment-emergent SAEs** with higher incidence in the sorafenib + BSC group in the SAF population were (sorafenib + BSC versus placebo + BSC group): infection with normal ANC, lung (pneumonia) (3.2% versus 1.1%), death not associated with CTCAE term, disease progression NOS (5.8% versus 3.7%), and constitutional symptoms - other (specify) (2.9% versus 1.1%).

Treatment emergent AEs leading to death (grade 5) were more common in the sorafenib + BSC group than in the placebo + BSC group: 80 (23.1%) versus 46 (13.1%) patients, respectively, in the SAF population. In the SAF population, deaths within 30 days after end of study medication were reported for 22.8% of the patients in the sorafenib + BSC group and for 12.5% in the placebo + BSC group.

The most common grade 5 AEs by CTCAE category in the sorafenib + BSC versus the placebo + BSC group were pulmonary/upper respiratory events (7.5% versus 7.1%), death (7.2% versus 4.0%), and infection (2.0% versus 0.9%). The most common grade 5 pulmonary/upper respiratory TEAE was dyspnea (6.4% versus 5.7%), and the most common TEAE reported as

death was death not associated with CTCAE term, disease progression NOS (5.8% versus 3.7%). Most fatal infections affected the airways, i.e., lung, bronchus, or the upper airway.

Grade 5 SAEs were reported in 23.1% versus 13.1% of the patients, respectively. Of these, 1.4% patients in the sorafenib + BSC group and none of the patients in the placebo + BSC group had sorafenib/placebo-related SAEs.

Treatment-emergent AEs led to discontinuation of study medication slightly more often in the sorafenib + BSC group (12.4%) than in the placebo + BSC group (6.3%) in the SAF population.

Overall, the most common TEAEs leading to discontinuation were dermatology/skin events: 11(3.2%) patients in the sorafenib + BSC group and 2 (0.6%) in the placebo + BSC group. Of these, the most common were hand-foot skin reactions (2.3% versus 0.3%). Pulmonary/upper respiratory events were the next most common reasons: 4 (1.2%) and 6 (1.7%) patients, respectively. Of these, the most common AE was dyspnea in 2 (0.6%) versus 5 (1.4%) patients, respectively.

Dermatology/skin events were the **most common TEAEs leading to dose reductions** in the SAF population (22.0% versus 0.3%). Dose interruptions were also most commonly due to dermatology/skin events (27.2% versus 0.9%).

In the **laboratory analyses**, the most common grade 3 hematological abnormalities were those affecting lymphocytes with slightly higher incidence in the sorafenib + BSC group compared to the placebo + BSC group (9.2% versus 3.4%). All other grade 3 and 4 hematological abnormalities were rarely registered, i.e., in not more than in 0.9% of the patients in either treatment group. In the SAF population, grade 3 hypophosphatemia was the most common biochemical abnormality group (14.2% versus 2.3%).

The **ECOG status** was 0 or 1 for all but one l patient at screening. For most of the patients in both treatment groups, the ECOG status had not changed during treatment: 53.0% patients in the sorafenib + BSC group and 56.8% patients in the placebo + BSC group in the FAS population.

Other evaluations

Tumor and/or plasma mutation data were available from 347 patients (49% of the study population). EGFR and Proto-oncogene V-Ki-ras2 Kirsten rat sarcoma viral oncogene

Homolog (KRAS) mutations were detected in 89 (26%) and 68 (20%) patients, respectively, and were well balanced between treatment arms. Analysis of the interaction between EGFR mutation status and treatment effect on survival suggested that patients with EGFR mutations benefitted from sorafenib, while those with wild-type EGFR did not ($p = 0.023$). Median OS was 2-fold longer in patients with EGFR mutations receiving sorafenib than in those receiving placebo (423 versus 197 days; HR = 0.48; $p = 0.002$). In patients with wild-type EGFR there was no significant survival difference between treatment arms (HR = 0.92; $p = 0.559$). Similar findings resulted from analysis of the interaction of EGFR mutations with sorafenib effect on PFS ($p = 0.015$), where patients with EGFR mutations (HR = 0.27; $p<0.001$) benefitted more from sorafenib treatment than those without (HR = 0.62; $p<0.001$). KRAS mutation status was not predictive of sorafenib efficacy.

These exploratory genetic biomarker analyses suggest that advanced NSCLC patients with EGFR mutations may derive survival benefit from receiving 3rd/4th line sorafenib. However, these results must be interpreted with caution due to the retrospective nature of the analyses and to the small, non-representative composition of the genetic biomarker subpopulation analyzed in this

trial. Any identified correlates of sorafenib response would need to be confirmed in a separate trial and would require further study to determine predictive or clinical utility.

Updated information after 16 Mar 2012

Updated safety results for 10 patients who were still receiving study medication after 16 MAR 2012 until the last patient last visit on 2 APR 2013 (the data-cut-off date for this last patient was 24 Apr 2013) were reported. In addition, any new or updates to serious adverse events (SAEs) were presented in narratives for these patients.

Summary of updated safety results of the addendum report:

Two patients had SAEs:

One patient with WORSENING of DYSPNEA (CTCAE Grade 2), BRONCHOPNEUMONIA (Grade 3), followed approximately 5 months later by an episode of MIGRAINE headache (CTCAE grade 3). All events were reported to have resolved with remedial drug therapy. The events were considered unrelated to study drug by both the investigator and the sponsor. This patient terminated the study on 07 FEB 2013 due to transferal to the treatment discontinuation study.

One patient with TRANSIENT ISCHEMIC ATTACK (TIA) (CTCAE Grade 4), CIRCILATORY COLLAPASE (Grade 5), RESPIRATORY FAILURE (Grade 5). These SAEs resulted in the death of the patient. The events were considered unrelated to study drug treatment by both the investigator and the sponsor but was judged to be due to the patient's underlying disease.

One patient had events that were considered of interest:

One patient with two episodes of HYPERURICEMIA (CTCAE Grade 4). Both occurrences of these events were reported to have resolved following remedial drug therapy and were not considered to be related to the study drug treatment by either the investigators or the sponsor. This patient was also reported to have developed ENDOMETRIAL CANCER (CTCAE Grade 3) considered as unrelated to the study drug. The patient developed progressive disease of non-small cell lung cancer and discontinued participation in the study.

Extended narratives were prepared for 7 patients were also prepared for the other 7 patients who were still receiving study drug treatment after the data cut-off date of 16 MAR 2012. Adverse events (AEs) that were considered by the investigator as related to study drug and that occurred or continued after 16 MAR 2012 were reported for the following 4 patients.

One patient with RASH ON LEGs (CTCAE Grade 1) reported to have resolved and SKIN BLISTERS UPPER and LOWER LEGs (CTCAE Grade 1) reported as ongoing. The last day of study drug treatment for this patient was 08 JAN 2013. The primary reason for termination of study for this patient was transferral to the treatment continuation study.

One patient with ALOPECIA(CTCAE Grade 1). This event was reported to have resolved after 9 months. The patient discontinued the study due to progressive disease on 20 Sep 2012. The last day of study drug treatment for this patient was on 4 AUG 2011.

One patient with HAND FOOT SKIN REACTION (CTCAE Grade 1) resolved after 2 weeks, HYPOPHOSPHATEMIA (CTCAE Grade 2) resolved after 3 weeks, and MUCOSITIS of THE ORAL CAVITY (CTCAE Grade 1) resolved after 4 weeks. The last day of study drug treatment for this patient was 01 APR 2013. The primary reason for termination of study for this patient was transferral to the treatment continuation study.

One patient with ongoing FATIGUE (CTCAE Grade 2) with outcome unchanged after dose of study drug was reduced and two episodes of DIARRHEA (CTCAE Grade 2) [resolved after dose of study drug reduced and remedial drug therapy] and CTCAE Grade 1 [unchanged after remedial drug therapy]). The last day of study drug treatment for this patient was 18 DEC 2012. The primary reason for termination of

study was disease progression.

Of these 7 patients, 3 discontinued the study due to progressive disease and 4 patients discontinued due to transferal to the treatment continuation study.

Conclusion(s)

The study did not meet its primary endpoint. There was no benefit in OS with sorafenib as a monotherapy for patients who had received 2 to 3 previous treatments for advanced, non-squamous NSCLC.

In the secondary endpoint analyses based on investigators' assessments, there was a statistically significant improvement of the PFS and prolongation of TTP.

No significant differences in patient's global health status/quality of life and functioning (physical and emotional) were observed between the two treatment groups.

The adverse events reported under sorafenib treatment were in general as expected and were manageable with best supportive care. There were no new or previously unreported significant toxicities reported during this study.

Publication(s):	None		
Date Created or Date Last Updated:	06 Mar 2014	**Date of Clinical Study Report:**	5 Nov 2012 (original report) 11 Jan 2013 (amended) 18 Nov 2013 (addendum)

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. H Olschewski	Medizinische Universität Graz	Auenbruggerplatz 20	8036	Graz	Austria
2	Dr. K Aigner	Krankenhaus der Elisabethinen Linz	Pneumologische Abteilung Fadingerstr. 1	4010	Linz	Austria
3	Dr. P COLLARD	CU Saint-Luc/UZ St-Luc	Service Pneumology/ Dienst Pneumologie Avenue Hippocrate 10 Hippocrateslaan	1200	BRUXELLES - BRUSSEL	Belgium
4	Dr. M THOMEER	Ziekenhuis Oost-Limburg	Campus Sint-Jan Departement Pneumologie Schiepse Bos 6	3600	GENK	Belgium
5	Dr. B COLINET	Grand Hôpital de Charleroi	Site Clinique Notre-Dame Grand'Rue 3	6000	CHARLEROI	Belgium
6	Assoc. Prof. A Dudov	District Dispensary for Oncology Diseases with Inpatient	Andrey Saharov blvd 1	1784	Sofia	Bulgaria
7	Assoc. Prof. D Damyanov	Specialized Hospital for Active Treatment of Oncology	Chemotherapy Department Plovdisko Pole 6 Street		Sofia	Bulgaria
8	Dr. P Petrov	District Dispensary for Oncology Diseases with Inpatient	Department of Drug oncotherapy and palliative care		Plovdiv	Bulgaria
9	Dr. V Taskova	Interdistrict Dispensary for Oncological Diseases Dr.M.Marko	Tsar Osvoboditel 100 Blvd.	9002	Varna	Bulgaria

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
10	Assoc. Prof. D Kalev	MHAT Sveta Marina EAD	Clinic of Oncology Hristo Smirnenski 1, Blvd	9010	Varna	Bulgaria
11	Dr. J Rodrigues Pereira	Grupo de Assistencia Medica e Prestacao de Servicos Ltda	Rua Martinico Prado, 26 12th floor room 125 Higienopolis	01224-010	Sao Paulo	Brazil
12	Dr A A Lima	Hospital e Maternidade Brasil	Rua Coronel Fernando Prestes 1177 Vila Dora	09020 110	Santo André	Brazil
13	Dr A C Andrade	BioCancer	Av. Bernardo Monteiro 918	30150-281	Belo Horizonte	Brazil
14	Dr. C H Barrios	Hospital Sao Lucas da Pontificia Universidade Catolica do RS	Hospital Sao Lucas Centro de Pesquisa em Oncologia Av. Ipiranga, 6690 4th floor	90610-000	Porto Alegre	Brazil
15	Dr. O Smaletz	Hospital Israelita Albert Einstein	Sociedade Beneficente Israelita Brasileira Instituto de Ensino e Pesquisas Av. Albert Eisntein, 627/701 - 2 subsolo	05651-900	São Paulo	Brazil
16	MD R P Pereira	Irmandade Santa Casa de Misericordia de Porto Alegre	Núcleo de Novos Tratamentos em Cancer Rua Sarmento Leite, 187 - 3 andar	90050 170	Porto Alegre	Brazil
17	Md H Z Fernandes	Instituto de Oncologia do Vale	Rua Major Antonio Domingues, 472 - Centro	12245750	São José dos Campos	Brazil
18	Dr. V Hirsh	McGill University	Department of Oncology 546 Pine Avenue West	H2W 1S6	Montreal	Canada
19	Dr. O Aren	Instituto Nacional del Cancer	Av. Profesor Zañartu 1010 Independencia	838-0455	Santiago	Chile
20	Dr. M Ahumada	Hospital Clínico Universidad de Chile	Servicio de Oncologia, Sector B, Piso 1 Santos Dumont N 999 Independencia	838-0456	Santiago	Chile
21	Prof Y Sun	Cancer Hospital, Chinese Academy of Medical Sciences	Oncology Medicine, No.17 Pan Jia Yuan	100021	Beijing	China
22	Dr Y WU	Guangdong General Hospital	Oncology Dept. No.106, Zhongshan er Road	510080	Guangzhou	China
23	Prof. L ZHANG	Sun Yat-sen University Cancer Center	Oncology medicine, No.651, Dongfengdong Road	510060	Guangzhou	China
24	Prof M Liao	Shanghai Chest Hospital, Shanghai Jiaotong University	Oncology Dept. No.241, Huaihai Xi Road	200030	Shanghai	China
25	Dr C Zhou	Shanghai Pulmonary Hospital, Tongji University	Oncology Dept. No.507, Zhengmin Road	200433	Shanghai	China

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
26	Prof. S QIN	PLA 81 Hospital	Floor 9, Inpatient Building, Department of Cancer, No.34, 34 Biao Yanggongjing Street	210002	Nanjing	China
27	Dr J WANG	Peking University Cancer Hospital	No.52, Fucheng Road, Haidian District,	100142	Beijing	China
28	Dr S JIAO	Chinese PLA General Hosp.	Oncology Dept. No.28, Fuxing Road, Haidian District	100853	Beijing	China
29	Dr X LIU	307 Hospital of PLA	Section 4 of Cancer Department/ Floor 5 of Internal Medicine Building, No.8 of Dong Da Jie, Fengtai District.	100071	Beijing	China
30	Prof H Pan	Sir Run Run Shaw Hospital	Oncology dept. No.3, Qingchun East Road	310016	Hangzhou	China
31	Dr Y Zhang	Zhejiang Cancer Hospital	No.38, Guangji Road, Banshanqiao	310022	Hangzhou	China
32	Dr Y LU	West China Hospital, Sichuan University	37 Guoxue Lane	610041	Chengdu	China
33	Dr. M Reck	Krankenhaus Grosshansdorf	Zentrum für Pneumologie und Thoraxchirurgie Onkologischer Schwerpunkt Wöhrendamm 80	22927	Großhansdorf	Germany
34	Dr. J von Pawel	Asklepios Fachkliniken München Gauting	Onkologie Robert-Koch-Allee 2	82131	Gauting	Germany
35	Dr. W Engel-Riedel	Kliniken der Stadt Köln - Städt. Krankenhaus Köln-Merheim	Lungenklinik - Haus 23/24 Ostmerheimer Straße 200 Köln Nordrhein-Westfalen	51109	Köln	Germany
36	Hr. Prof. Dr. M Thomas	Thoraxklinik-Heidelberg gGmbH	Onkologie Amalienstr. 5	69126	Heidelberg	Germany
37	Hr. Prof. Dr. J Mezger	St. Vincentius-Kliniken gAG	Medizinische Klinik II Hämatologie, Onkologie, Immunologie Südendstr. 32	76137	Karlsruhe	Germany
38	Hr. Dr. C Schneider	Zentralklinik Bad Berka GmbH	Abteilung für Hämatologie und Onklolgie Robert-Koch-Allee 9 Bad Berka Thüringen	99437	Bad Berka	Germany
39	Hr. Prof. Dr. J Greiner	Universitätsklinikum Ulm	Innere Medizin III Hämatologie/Onkologie Albert-Einstein-Allee 23	89091	Ulm	Germany
40	Dr. L Paz Ares	Hospital Universitario Virgen del Rocío	Servicio de Oncología Av. Manuel Siurot, s/n	41013	Sevilla	Spain
41	Dr. M Cobo	Hospital Regional Carlos Haya	Servicio de Oncología Médica Avda. Carlos Haya s/n	29010	Málaga	Spain

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
42	Dra. T de Portugal	Complejo Hospitalario de Zamora	Servicio de Oncología C/ Hernán Cortés,40	49021	Zamora	Spain
43	Dr. G López Vivanco	Hospital de Cruces	Servicio de Oncología Pza. de Cruces, s/n	48903	Cruces/Barakaldo	Spain
44	Dra. C Pallarés	Hospital de la Santa Creu i de Sant Pau	Servicio de Oncología C/Mas Casanovas, 90	08025	Barcelona	Spain
45	Dra. N Viñolas	Hospital Clínic i Provincial de Barcelona	Servicio de Oncología Médica C/ Villarroel, 170	08036	Barcelona	Spain
46	Dr. D Márquez	Hospital Universitario Arnau de Vilanova de Lleida	Servicio de Oncología Av. Alcalde Rovira Roure, 80, planta edificio viejo	25198	Lleida	Spain
47	Dr. S Vázquez	Hopsital Lucus Agustí	Servicio de Oncología Médica c/ san Cibrao s/n	27003	Lugo	Spain
48	Dr. J Fírvida	Complejo Hospitalario de Orense	Hospital Santa María Nai Servicio de Oncología c/ Ramón Puga, 54, 1ª planta	32005	Orense	Spain
49	Dr B COUDERT	Centre Georges Francois Leclerc Dijon	Centre Georges Francois Leclerc 1 rue du Professeur Marion	21000	DIJON	France
50	Docteur J BENNOUNA	Centre René Gauducheau - Nantes	Centre René Gauducheau Boulevard Jacques Monot	44805	SAINT HERBLAIN	France
51	Pr J GUERIN	Hôpital de la Croix Rousse	Hospices Civils de Lyon Hôpital de la Croix Rousse Service des Maladies Infectieuses 93, rue de la Grande Croix Rousse	69317	LYON CEDEX	France
52	Dr E Pichon	Hôpital Bretonneau - Tours	Hôpital Bretonneau Service de Neurologie 2, boulevard de la Tonnelle	37044	TOURS	France
53	Dr E DANSIN	Centre Oscar Lambret	Centre Oscar Lambret 3 rue frederic combemale BP 307	59020	Lille	France
54	Docteur D MORO-SIBILOT	Center Hospitalier Michallon - Grenoble	Centre Hospitalier Universitaire - Hopital Michallon Département de Médecine Aigüe Spécialisée Pneumologie BP 217	38700	LA TRONCHE	France
55	Docteur R GERVAIS	Centre François Baclesse - CLCC - Caen	Centre François Baclesse Avenue du Général Harris B.P. 5026	14073	CAEN	France

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
56	Dr T CHATELLIER	Centre Hospitalier Départemental-La Roche sur Yon	Centre Hospitalier Départemental Les Oudairies Service de Cardiologie 85025 LA ROCHE SUR YON CEDEX	85025	LA ROCHE SUR YON CEDEX	France
57	Dr M O'Brien	Royal Marsden NHS Trust (Surrey)	Department of Medical Oncology Downs Road	SM2 5PT	Sutton	United Kingdom
58	Mr S Popat	Royal Marsden Hospital (London)	Department of Medical Oncology 1st Floor Mullberry House Fulham Road	SW3 6JJ	London	United Kingdom
59	Dr M Nicolson	Aberdeen Royal Infirmary	Department of Clinical Oncology Aberdeen Royal Infirmary Forresthill	AB25 2ZN	Aberdeen	United Kingdom
60	Dr C Mulatero	St James' University Hospital	St James Oncology Centre Beckett Street Bexley Wing	LS9 7TF	Leeds	United Kingdom
61	Prof T Eisen	Addenbrookes Hospital	Cambridge Cancer Trials Centre Oncology Clinical Trials (S4) Box 279	CB2 0QQ	Cambridge	United Kingdom
62	Dr D Chao	Royal Free Hospital	Department of Medical Oncology Pond Street Hampstead	NW3 2QG	London	United Kingdom
63	Dr F Blackhall	Christie Hospital	CRC Department of Medical Oncology, Christie CRC Research Centre Christie Hospital NHS Trust 550 Wilmslow Road Withington	M20 4BX	Greater Manchester	United Kingdom
64	Dr J Braybrooke	Southmead Hospital	Lung Research Group Westbury on Trym	BS10 5NB	Bristol	United Kingdom
65	Prof. V Georgoulias	University General Hospital of Heraklion	General University Hospital of Heraklion, Voutes	711 10	Heraklion	Greece
66	Prof. Dr. C Syrigos	Sotiria General State Hospital of Chest Diseases	152, Messogion Avenue	11527	Athens	Greece
67	Prof. C Zarogoulidis	G. Papanikolaou General Hospital of Thessaloniki	Exohi	570 10	Thessaloniki	Greece
68	Prof T MOK	Prince of Wales Hospital	Department of Clinical Oncology Rm 418/F, Cancer Centre		Shatin	Hong Kong

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
69	Dr J Ho	Queen Mary Hospital	Division of Respiratory & Critical Care, Department of Medicine,		Hongkong	Hong Kong
70	Dr M Gyulai	Pest County Lung Institute	Tudogyogyintezet Munkacsy Mihaly u. 70	2045	Torokbalint	Hungary
71	Dr. S Tehenes	Zala Megyei Korhaz	Dept. of Oncology Kulso-Korhaz u.1	8900	Zalaegerszeg	Hungary
72	Dr E Juhasz	Orszagos Koranyi TBC es Pulmonologiai Intezet	Pihenõ u. 1.	1529	Budapest	Hungary
73	Dr. B Medgyasszay	Veszprem County Pulmonology Institute	n/a	8582	Farkasgyepu	Hungary
74	Dr. A Bartos	Koch Robert Hospital	I. Pulmonology Danko Pista u. 80	3780	Edeleny	Hungary
75	Prof. G Losonczy	University of Semmelweis	Pulmonology Clinic Diosarok u. I/c	1125	Budapest	Hungary
76	Dr N Sutandyo	National Cancer Center DHARMAIS	Jl. Letjen S. Parman Kav. 84-86	11420	Jakarta	Indonesia
77	Dr. M Gottfried	Meir Medical Center	59 Tchernichovsky Street	4428164	Kfar Saba	Israel
78	Dr. H Hayat	Edith Wolfson Medical Center	Oncology Department Edith Wolfson Medical Center		Holon	Israel
79	Dr. A Cyjon	Assaf Harofeh Medical Center	Oncology Department	6093000	Zrifin	Israel
80	Dr. S Stemmer	Rabin Medical Center - Beilinson Campus	Oncology Department	4941492	Petach Tikva	Israel
81	Dr. T E Tichler	Shaare Zedek Medical Center	Oncology Department Shaare Zedek Medical Center	9372212	Jerusalem	Israel
82	Dr. N Ramu	Hadassah Hebrew University Hospital Ein Kerem	Ongology Department Hadassah Ein Karem	9112001	Jerusalem	Israel
83	Dr R Nagarkar	Curie Manavata Cancer Centre	Opp. Mahamarg Bus Stand	422004	Mumbai	India
84	Dr G Vadavattan	Lakeshore Hospital and Research Center Ltd	NH-47 By-Pass, Maradu, Nettoor, P.O. Kochi.	682304	Kerala	India
85	Dr M Jain	Ruby Hall Clinic	40 Sasson Road	411001	Pune	India
86	Dr. A Santoro	IRCCS Istituto Clinico Humanitas	Oncologia Medica ed Ematologia Via Manzoni, 56	20089	Rozzano	Italy
87	Prof. F De Marinis	A.O. San Camillo-Forlanini	Pneumologia Oncologica 1 Dip. Malattie Polmonari Piazza Forlanini, 1	00151	Roma	Italy

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
88	Prof. L Crinò	A.O.U. di Perugia	Oncologia Medica Ospedale Santa Maria della Misericordia Via G. Dottori, 1 - Località S.Andrea delle Fratte	06156	Perugia	Italy
89	Dr. M Tiseo	A.O.U. di Parma	Oncologia Medica Via Gramsci,14	43100	Parma	Italy
90	Dr. F Cappuzzo	AUSL 06 Livorno - Toscana	Oncologia Medica P.O. di Livorno Viale Alfieri, 36	57124	Livorno	Italy
91	Dr. S Novello	A.O.U. San Luigi Gonzaga	Oncologia Polmonare Regione Gonzole, 10	10043	Orbassano	Italy
92	Dr. P Bidoli	A.O. San Gerardo di Monza	Oncologia Medica Via Pergolesi, 33	20052	Monza	Italy
93	Prof. C Gridelli	A.O. San Giuseppe Moscati	Oncologia Medica Via Circumvallazione, 68	83100	Avellino	Italy
94	Dr. F Grossi	IRCCS Ist Nazionale Tumori GE	Oncologia Medica Largo R. Benzi, 10	16132	Genova	Italy
95	Prof. K Eguchi	Teikyo University Hospital	Medical Oncology 2-11-1, Kaga	173-8606	Itabashi-ku	Japan
96	Dr. M Nishio	The Cancer Institute Hospital of JFCR	Respiratory Tract Medicine 3-8-31 Ariake	135-8550	Koto-ku	Japan
97	Dr. I Okamoto	Kinki University Hospital	Medical Oncology 377-2, Ohnohigashi	589-8511	Osakasayama	Japan
98	Dr. S Atagi	Kinki-Chuo Chest Medical Center	Internal Medicine 1180 Nagasone-cho Kita-ku	591-8555	Sakai	Japan
99	Dr. M Satouchi	Hyogo Cancer Center	Thoracic Oncology 13-70 Kitaoji-cho	673-8558	Akashi	Japan
100	Dr. T Seto	National Kyushu Cancer Center	Department of Thoracic Oncology 3-1-1 Notame Minami-ku	811-1395	Fukuoka	Japan
101	Dr. S Niho	National Cancer Center Hospital East	Thoracic Medical Oncology 6-5-1 Kashiwanoha	277-8577	Kashiwa	Japan
102	Dr. T Hida	Aichi Cancer Center Hospital	Department of Respiratory Medicine 1-1 Kanokoden Chikusa-ku	464-8681	Nagoya	Japan
103	Dr. Ph.D S Kim	Asan Medical Center	88, OLYMPIC-RO 43-GIL, SONGPA-GU	138-736	Seoul	Korea, Republic Of
104	Dr S Shin	Korea University Anam Hospital	73, Inchon-ro 7-gil, Seongbuk-gu	136-705	Seoul	Korea, Republic Of
105	Dr J Kang	Seoul St. Mary's Hospital	222 BANPO-DAERO, SEOCHO-GU,	137-701	Seoul	Korea, Republic Of
106	Dr D Kim	Seoul National University Hospital	101 DAEHAK-RO JONGNO-GU	110-744	Seoul	Korea, Republic Of

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
107	Dr K park	Samsung Medical Center	81 Irwon-Ro Gangnam-gu. Seoul	135-710	Seoul	Korea, Republic Of
108	Mrs. Dr. J Herder	St. Antonius Ziekenhuis	Afdeling Longziekten Koekoekslaan 1	3435 CM	NIEUWEGEIN	Netherlands
109	Dhr. Prof. E Smit	Vrije Universiteit Medisch Centrum	Academisch Ziekenhuis Vrije Universiteit - Afd. Longziekten - De Boelelaan 1117	1081HV	Amsterdam	Netherlands
110	Dhr. J Stigt	Isala Klinieken, Locatie Sophia	Afdeling Longziekten, Dr. van Heesweg 2	8025 AB	ZWOLLE	Netherlands
111	Dhr. Dr. F Custers	Atrium Medisch Centrum Parkstad	Afdeling Longziekten, H.Dunantstraat 5	6419 PC	HEERLEN	Netherlands
112	Dr. S Gans	Ziekenhuis St. Jansdal	St. Jansdal - Longziekten - Weth. Jansenlaan 90	3844 DG	HARDERWIJK	Netherlands
113	Drs. W Pieters	Elkerliek Ziekenhuis, Lokatie Helmond	Elkerliek Ziekenhuis - Afd. Longziekten - Wesselmanlaan 25	5707 HA	HELMOND	Netherlands
114	Mr. Dr. L Riva González	Hospital Edgardo Rebagliati Martins	Av. Edgardo Rebagliati Martins S/N JESUS MARIA	LIMA 11	Lima	Peru
115	Mrs. Dr. P R Pimentel Álvarez	Hospital Alberto Sabogal Sologuren	Avenida Colina 1081	CALLAO 2	Callao	Peru
116	Mr. Dr. J S Guevara Guevara	Hospital Nacional Guillermo Almenara Irigoyen	Av. Grau 800	LIMA 1	Lima	Peru
117	Dr V Chan	Veterans Memorial Medical Center	Cancer Research Center North Avenue	1104	Quezon City	Philippines
118	Dr D Tudtud	Perpetual Succour Hospital	Cebu Cancer Institute, F. Sotto Drive	6000	Cebu City	Philippines
119	Dr P Caguioa	Santo Tomás University Hospital	Benavidez Cancer Institute Espana Blvd.	1000	Manila	Philippines
120	Dr A Villalon	Manila Doctors Hospital	Dona Salustiana Building, 667 United Nations Avenue, Ermita	1000	Metro Manila	Philippines
121	Dr J Mallick	Dr Ziauddin Hospital	Department of Oncology Block-B North Nazimabad	74700	Karachi	Pakistan
122	Dr S Ahmed	Mayo Hospital	Department of Radiation Oncology Neeela Gumbad	54000	Lahore	Pakistan
123	Dr. I Cedrych	Centrum Onkologii Instytut im. M. Sklodowskiej-Curie	Klinika Nowotworow Ukladowych i Uogolnionych ul. Garncarska 11	31-115	Krakow	Poland
124	Prof. K Roszkowski-Sliz	Instytut Gruzlicy i Chorob Pluc	Instytut Gruzlicy i Chorob Pluc III Klinika Chorób Pluc ul. Plocka 26	01-138	Warszawa	Poland
125	Dr A Mruk	NZOZ MRUKMED 2 Sp. p., Przychodnia Specjalistyczna	ul. Langiewicza 61	35-021	Rzeszow	Poland

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
126	Dr. A Kazarnowicz	Samodzielny Publiczny Zespól Gruzlicy i Chorób Pluc	Oddzial V Chemioterapii Nowotworow Pluc, ul. Jagiellonska 78	10-357	Olsztyn	Poland
127	Dr P Serwatowski	Specjalistyczny Szpital im. prof. Alfreda Sokolowskiego	ODDZIAL II ONKOLOGII KLINICZNEJ I CHEMIOTERAPII ul. A. Sokolowskiego 11	70-891	Szczecin	Poland
128	Prof. M Y Biakhov	Railways Hospital named after Semashko	Budaiskaya 2	129128	Moscow	Russia
129	Prof. V Gorbunova	Russian Oncological Scientific Center n.a. N.N. Blokhin RAMS	Department of Chemotherapy 19th floor 24, Kashirskoe shosse	115478	Moscow	Russia
130	Prof. R S Khasanov	Clinical Oncology Dispensary	Sibirskiy tract, 29	420029	Kazan	Russia
131	Dr N A Karaseva	City Clinical Oncology Center	Department of Thoracic surgery Veteranov prospect 56	198255	St. Petersburg	Russia
132	Prof. A M Garin	Russian Oncological Scientific Center n.a. N.N. Blokhin RAMS	Kashirskoe sh., 24	115478	Moscow	Russia
133	Dr B Bergman	Sahlgrenska Universitetssjukhuset	Lungonkologisk mottagning Vita stråket 12	413 45	Göteborg	Sweden
134	Dr A Vikström	Universitetssjukhuset i Linköping	Universitetssjukhuset i Linköping Lungmedicinska kliniken	581 85	Linköping	Sweden
135	Dr R Öhman	Skånes Universitetssjukhus	Lungmedicinens Dagvård	221 85	Lund	Sweden
136	Dr K Kölbeck	Karolinska Universitetssjukhuset i Solna	Karolinska Universitetssjukhuset i Solna Lung- och allergikliniken	171 76	Stockholm	Sweden
137	Dr P Sobrino	Falu Lasarett	Lungmottagningen Medicinkliniken	791 82	Falun	Sweden
138	Dr. R Soo	National University Cancer Institute, Singapore	NUHS Tower Block Level 7 IE Kent Ridge Road	119228	Singapore	Singapore
139	Dr G Lopes	Johns Hopkins Singapore IMC	Johns Hopkins Singapore, International Medical Centre, 11 Jalan Tan Tock Seng,	308433	Singapore	Singapore
140	Prof. S Thongprasert	Maharaj Nakorn Chiang Mai Hospital	Department of Internal Medicine, Faculty of Medicine, 110 Intravarorot Road, Sripum, Muang,	50200	Chiang Mai	Thailand

No	Investigator Name	Facility Name	Street	ZIP Code	City	Country
141	Assis.Prof. V Srimuninnimit	Siriraj Hospital, Mahidol	Division of Medical Oncology, Department of Medicine, 13 th Fl. Chalerm-Prakiat Building, Faculty of Medicine Siriraj Hospital Bangkok-noi	10700	Bangkok	Thailand
142	Dr A Dechapunkul	Prince of Songkla University	Medical Oncology Unit Department of Medicine,15 Karnjanavanit Road, Hat Yai,	90110	Songkhla	Thailand
143	Prof. T Goksel	Ege Universitesi Tip Fakultesi	Gogus Hastaliklari Anabilim Dali		Izmir	Turkey
144	Prof. P F Yumuk	Marmara University Medical Faculty	Tibbi Onkoloji Bilim Dali Altunizade 34662 Uskudar	34662	INSTANBUL	Turkey
145	Prof. M Ozguroglu	Istanbul Universitesi Cerrahpasa Tip Fakultesi	Tibbi Onkoloji Bilim Dali Cerrahpasa		Istanbul	Turkey
146	Prof. H Onat	Anadolu Saglik Merkezi	Onkolojik Bilimler Merkezi Gebze 41400	41400	Kocaeli	Turkey
147	Prof. G Utkan	Ankara Universitesi Tip Fakultesi	Tibbi Onkoloji Bilim Dali 06100 Cebeci		Ankara	Turkey
148	Prof C Yang	National Taiwan University Hospital	National Taiwan University Hospital No 7 Chung-Shan South Road,	10016	Taipei	Taiwan
149	Dr H Kuo	Chang Gung Memorial Hospital at Linkou	No5, Fu-Hsing Street, Kuei Shan Shiang	333	Taoyuan	Taiwan
150	Dr. G Chang	Taichung Veterans General Hospital	160,Sec 3,Tai-Chung-Kang Rd	40705	Taichung	Taiwan
151	Dr T Hsia	China Medical University Hospital	No. 2, Yuh-Der Rd.	404	Taichung	Taiwan
152	Dr M Huang	Kaohsiung Medical University Hospital	No.100, Shih-Chuan 1st Road	80756	Kaohsiung	Taiwan
153	Dr. J T Beck	Highlands Oncology Group	3232 N.North Hills Blvd.	72703	Fayettevill e	United States
154	Dr. H Wakelee	Stanford Hospital & Clinics	Stanford Cancer Center 875 Blake Wilbur Drive	94305	Stanford	United States
155	Dr R M Khanyile	University of Pretoria, Prinshof Campus	Prinshof Campus Department of Medical Oncology	0084	Prietoria	South Africa
156	Dr K I Maart	Langehoven Drive Oncology Centre	GVI Oncology 1 Mangold Street Newtown Park	6045	Port Elizabeth	South Africa
157	Dr W M Szpak	Dr Pirjol, Szpak 7 Moodley	315 Ipahla Road Athlone Park Amanzimtoti	4126	Durban	South Africa

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