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 Pharmaceuticals Inc.	
Study Number:	11848	NCT00117637
Study Phase:	II	
Official Study Title:	A randomised, open-label, multi-center phase II study of first-line treatment with BAY 43-9006 (Sorafenib) versus standard treatment with Interferon alpha-2a in subjects with unresectable and/or metastatic renal cell carcinoma	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Sorafenib (Nexavar, BAY43-9006)	
Name of Active Ingredient:	Sorafenib	
Dose and Mode of Administration:	Subjects received 2 tablets of sorafenib (200 mg tablets) twice daily (i.e., 12-hourly) or, after increasing the dose to 600 mg bid, 3 tablets of sorafenib twice daily (i.e. 12-hourly) orally on a continuous basis.	
Reference Therapy/Placebo		
Reference Therapy:	Interferon alpha-2a (IFN α-2a)	
Dose and Mode of Administration:	IFN α-2a was administered at a dose of 9 million international units (MIU) subcutaneously (SC) three times a week. Subjects initially started with a single dose of 3 million international units (MIU) IFN α-2a and increased the dose as rapidly as possible to 9 MIU IFN α-2a three times a week within 1 (to 2) weeks.	
Duration of Treatment:	The treatment period included dosing twice daily in an uninterrupted schedule, but for the purpose of data recording, the treatment period was divided into cycles of 4 weeks duration. The treatment was continued until tumor progression or until unacceptable toxicity thought to be related to the study drug or to the standard therapy (IFN) was recorded.	
Studied period:	Date of first subjects' first visit:	14 JUN 2005
	Date of last subjects' last visit:	23 MAR 2009
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 20 SEP 2005) specified the changes which are listed below: • Corrected the actual stratification. • Changed "dose modification and delay of IFN α-2a". • Added the possibility of biomarker evaluation in tumor: cell differentiation [antigen] (CD)34, CD105 expression, vascular endothelial growth factor (VEGF)-C, hypoxia-inducible factor (HIF)-1α, HIF-2α, glucose transporter type-1 (Glut-1), carbonic anhydrase IX (CAIX), p53 mutational status, methylation status. • Added the possibility of biomarker evaluation in serum: VEGF-C, matrix metalloproteinase (MMP)-9. • Added the possibility of biomarker evaluation in plasma: VEGF-C.	

	• Added the evaluation in blood: circulating endothelial cells. Amendment no. 2 (dated 20 MAR 2006) specified the change which is listed below: • Clarified the Health Economics and Outcomes Research (HEOR) endpoints that were to be analyzed in this study. Amendment no. 3 (dated 10 MAY 2006) specified the change which is listed below: • The primary efficacy endpoint was progression free survival (PFS) assessed by independent radiological review unless the clinical progression was observed before the radiological progression.
Study Centre(s):	This multinational study included subjects enrolled from 31 centers in 6 countries: Germany (6), United States (7), France (5), Poland (6), Russia (3), UK (1) and Ukraine (3).
Methodology:	In this multi-center, multinational, open-label, active-controlled study, subjects were randomized and stratified by region and according to their prognostic category. Subjects receiving 400 mg bid sorafenib received a dose escalation to 600 mg bid following disease progression. Additionally, subjects receiving IFN who showed disease progression were crossed over to receive 400 mg bid sorafenib. Dose reduction was possible if toxicity was thought to be related to the study drug or to IFN. The end-of-treatment (EOT) visit was conducted 30 days after the last dose of study medication. Thereafter, subjects were entered into the follow-up period for the collection of survival status and concomitant anti-cancer therapy. Pharmacokinetic (PK) parameters were assessed prior to dosing at screening, on Day 1 of each cycle, at the EOT, and at the final visit only in the sorafenib treatment groups at 400 mg bid and 600 mg bid.
Indication/ Main Inclusion Criteria:	Indication: Unresectable and/or metastatic renal cell carcinoma (RCC) Main inclusion criteria: Men and women outpatients with histologically- or cytologically-confirmed, unresectable and/or metastatic, measurable predominantly clear cell renal cell carcinoma (RCC), who had received no prior systemic therapy, were enrolled in this study. Subjects with rare subtypes of RCC were excluded such as collecting duct or medullary, sarcomatoid, granular, papillary, chromophobe, small cell carcinoma, cystic RCC, rhabdoid variant of RCC and transitional cell cancer of the renal pelvis. Women and men with RCC were equally eligible according to sex prevalence for study participation. Inclusion in the study required fulfillment of all of the inclusion criteria and none of the exclusion criteria.
Study Objectives:	Overall: To evaluate the safety and efficacy of sorafenib versus IFN α-2a in subjects with unresectable and/or metastatic RCC. Primary:

	To compare the progression-free survival (PFS) time in two groups of randomized metastatic renal cell carcinoma (RCC) subjects receiving sorafenib 400 mg bid (SOR 400) versus standard therapy (IFN α-2a) as a first-line therapy. Secondary: • To evaluate overall response rate (RR) • To evaluate disease control rate (DCR) • To evaluate time to progression (TTP) • To evaluate duration of response (DOR) • To evaluate time to response (TTR) • To evaluate overall survival (OS) • To evaluate patient reported outcome (PRO) • To evaluate trough concentrations of sorafenib • To evaluate safety of patients • To evaluate biomarkers Tertiary: Correlation of biomarker results with key clinical endpoints. To compare computed tomography (CT)/Magnetic Resonance Imaging (MRI) scan volumetry vs computer-assisted evaluation per Response Evaluation Criteria in Solid Tumors (RECIST) vs standard radiological evaluation per RECIST.
Evaluation Criteria:	Efficacy (Primary): Progression-free survival (PFS) based on independent radiological review for the first intervention period. PFS was defined as the time from randomization to the first documented radiological disease progression or death (if death occurred before progression was assessed). For subjects without documented progression or death at the time of analysis, PFS was censored at the last date of tumor evaluation. Efficacy (Secondary): • PFS based on investigator assessment for the first and second intervention period • Disease control (DC), tumor response, duration of response, and time to response according to independent central review for the first intervention period and according to the investigator assessment for the first and second intervention period • Analysis of the Quality of Life (QoL) by use of the respiratory domain and total score of the Functional assessment of cancer therapy-Kidney Symptom Index (FKSI) after the first and second intervention period • Analysis of the QoL by use of Functional Assessment of Cancer Therapy-Biologic-Response Modifiers (FACT-BRM) for the first and second intervention period • Analysis of the treatment tolerability (effectiveness, side effects, convenience, and global satisfaction) by use of Treatment Satisfaction Questionnaire for Medication (TSQM) for the first and second intervention period • Overall Survival (OS) defined as the time from date of randomization to death due to any cause. Subjects alive at the time of analysis were censored at their last date of last contact • Analysis of the Eastern Co-operative Oncology Group (ECOG) status at the end of the first and second intervention period

	Efficacy (Tertiary): • Correlation of biomarker results with key clinical endpoints. • Comparison of CT/MRI scan volumetry vs computer-assisted evaluation per RECIST vs standard radiological evaluation per RECIST. Safety: Adverse events, laboratory changes (hematology, clinical chemistry and clinical urinalysis), changes in vital signs (blood pressure, heart rate), respiratory rate, temperature, and electrocardiogram (ECG).
	Pharmacokinetics: No pharmacokinetic parameters were calculated in this study as only trough concentrations for subjects treated with either 400 mg or 600 mg sorafenib bid were collected. Trough concentrations were collected at each cycle until the subject's disease progressed. The secondary outcome measures were: • Slope - change in trough concentration/cycle • Average of all trough plasma concentrations.
Statistical Methods:	Efficacy (Primary): All randomized subjects (intent-to-treat [ITT] Population) were included in the primary analysis. Subjects without tumor progression or death at the time of analysis were censored at their last date of evaluation. The analysis of the primary parameter (PFS) was carried out when approximately 140 PFS events were observed or when all subjects had at least 12 months of follow-up. The primary PFS analysis was based on independent radiological review. Two-sided alpha of 0.05 was used for analysis. No formal interim analysis was foreseen. Efficacy (Secondary): For secondary efficacy parameters, estimates of the objective tumor response rates, the disease control rates (DCRs) and their respective 95% confidence intervals (CIs) were computed for each treatment group. The rates were compared between treatment groups using the Chi-Squared Test. The primary analysis for patient reported outcome (PRO) was conducted on respiratory domain of Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-15), total score of FACT-BRM and the convenience domain of TSQM. Mixed effects model was used to assess the treatment differences between the treatment groups. Efficacy (Tertiary): Not available Safety: Descriptive summary tables were presented on all safety parameters by treatment group. Subjects were monitored for adverse events using the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) v 3.0. Treatment-emergent adverse events and safety laboratory parameters were summarized by treatment group and NCI-CTC v3.0

	grade.
	Pharmacokinetics : Potential changes in trough concentration over time were calculated using linear regression. Comparisons of sorafenib concentrations/exposure over time and across dose-levels were performed using descriptive statistics and plots.
Number of Subjects:	A total number of 160 subjects were panned to be enrolled in the study. However, as subject accrual was faster than expected, a total of 189 subjects were randomized within a time period significantly shorter than planned.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 221 enrolled subjects, 189 were randomized and 187 received at least 1 dose of study medication. All 189 subjects were included in the ITT population and all of them were included in the safety population, except for 2 subjects who were randomized in USA but did not receive study drug and were thus not considered valid for safety.

There were 52 males and 40 females in the IFN group and 65 males and 32 females in the sorafenib group. In the IFN group, race was White in 75 subjects and Asian in 1 subject. In the sorafenib group, race was White in 68 subjects. Race was not collected from the 45 subjects enrolled in France due to local regulations. Mean age in the IFN and sorafenib group was 61.8 years (range: 18–80 years) and 61.5 years (range: 34-78 years), respectively.

Results Summary — Efficacy

The primary endpoint of the study was PFS. Until the first cutoff date of 29 SEP 2006, the PFS analysis was based on blinded assessment of radiological scans by independent radiological review, applying RECIST criteria according to a prospectively approved radiology charter. Later on, no independent radiological review was performed and only the investigator assessment was reported.

A total of 189 subjects with advanced RCC not yet treated with any anti-cancer systemic therapy were randomized to IFN or sorafenib (SOR) 400. Randomization was prospectively stratified according to the region (East Europe, West Europe, and USA) and Motzer prognostic criteria. Results revealed that stratification and prognostic criteria were relatively balanced between the treatment groups. Results did not show an advantage of sorafenib versus IFN in terms of PFS. Based on the investigator's assessment of scans, median PFS was 7 months in subjects randomized to IFN and 5.6 months in subjects randomized to SOR 400. The estimated hazard ratio for progression (IFN over SOR 400) was 0.88 (P=0.47).

The median time to death was estimated to be 14.8 months for the SOR 400/600 group and to be 26.9 months for the IFN/SOR 400 group with a hazard ratio (IFN/SOR 400 over SOR 400/600) of 0.61 with the following confidence interval [0.41 – 0.91]. This may be interpreted that the OS of the latter group reflects basically 2 lines of therapy and thus is longer, while the prior group reflects only one line of therapy, though with dose escalation.

A total of 110 out of the 189 subjects (58.2%), went into the second period of the study. The descriptive analyses suggest a benefit of the cross over to sorafenib 400 mg bid for subjects who had progressed when treated with IFN. DCR was 50% in the dose escalation group, suggesting a benefit of increasing dosage after a progressive disease (PD).

Results Summary — Safety

During Period 1 (treatment with either SOR 400 or IFN as initial therapy), treatment-emergent adverse events were reported in 98% of subjects in the SOR 400 group and 96% of subjects in the IFN group, most of them were assessed as drug-related (95% for SOR 400 and 89% for IFN). The most common drug-related adverse events were hypertension, fatigue, anorexia, diarrhea, pain, alopecia, hand-foot skin syndrome, and rash/desquamation for SOR 400, and fever, fatigue, weight loss, anorexia, nausea, pain, and flu-like syndrome for IFN. Most of them occurred during the first 3 cycles of therapy and were of Grade 1 and 2.

Subjects who received the increased dose of SOR 600 after treatment with SOR 400 tolerated the dose increase well.

The incidence of subjects discontinuing the study drug due to adverse events was 25% for SOR 400 group and 22% for IFN group in Period 1, and 22% for IFN/SOR 400 group and 7% for SOR 400/600 group in Period 2.

Treatment-emergent serious adverse events were reported in 49% SOR 400 treated subjects and in 36% IFN treated subjects during Period 1 and were assessed as drug-related in 17% and 16% of subjects for the SOR 400 and IFN groups, respectively. The most common of them were diarrhea, hemorrhage, and hand-foot skin reaction for SOR 400 and fatigue, nausea and confusion for IFN. In Period 2, treatment-emergent serious adverse events were reported in 52% of subjects in the IFN/SOR 400 group and in 25% of subjects in the SOR 400/600 group, and were assessed as drug-related in 10% and 5% of subjects, respectively.

There were 39 deaths within 30 days of the last dose of study drug: 18 within Period 1 (14 for SOR 400 and 4 for IFN) and 21 within Period 2 (14 for IFN/SOR 400 and 7 for SOR 400/600). The most common cause of death was underlying RCC disease.

Based on the safety results, sorafenib was considered to be safe and well tolerated for the selected subject population and adverse events were clinically well manageable.

Results Summary — Pharmacokinetics

The median slopes of the log concentration vs time plots, for both parent drugs and metabolites, were negative in both the 400 mg and 600 mg dose levels and in both the 10-14 hour and 11-13 hour time intervals, suggesting a trend towards decreasing exposure. Due to the limited sampling in this study, the effect cannot be quantified in a pharmacokinetically or statistically relevant manner (confidence intervals included 1). Furthermore, there was a slight decrease in average concentration from the 400 mg to 600 mg dose level in both parent and metabolites (i.e., average concentration of BAY 73-4506 at 400 mg was –0.939 mg/L; at 600 mg was -0.804 g/L). However, the significance of this is not known.

Conclusion(s)			
In this study, subjects did not show a statistically significant improvement of progression-free survival of sorafenib versus interferon in first line treatment of renal cell carcinoma. Nevertheless, a higher disease control rate, a shorter time to response and a better quality of life were observed in the sorafenib group. A benefit of the crossover to sorafenib 400 mg bid for interferon subjects after progression was also suggested. Both study drugs were generally well tolerated, with an adverse events profile similar to that expected for both drugs and with a similar incidence of subjects discontinuing from the study due to adverse events in both the treatment groups.			
Publication(s):	Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, Negrier S, Laferriere N, Scheuring UJ, Cella D, Shah S, Bukowski RM. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009 Mar 10;27(8):1280-9. Epub 2009 Jan 26.		
Date Created or Date Last Updated:	13 APR 2012	Date of Clinical Study Report:	30 SEP 2009

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Pharma AG
Postal Address	D-13342 Berlin Deutschland
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Centre Léon Bérard	Centre Léon Bérard Service de Cancérologie Médicale 28 rue Laennec	69008	LYON CEDEX	FRANCE
2	Centre René Gauducheau - Nantes	Centre René Gauducheau Service d'Oncologie Médicale Boulevard Jacques Monot	44805	NANTES	FRANCE
3	Hopital Européen Georges Pompidou - Paris	Hopital Européen Georges Pompidou Service de Cancérologie Médicale du Professeur Andrieu 20-40 rue Leblanc	75908	PARIS CEDEX 15	FRANCE

4	Institut Gustave Roussy - Villejuif	Institut Gustave Roussy Unité immunothérapie 114 rue Edouard Vaillant	94805	VILLEJUIF	FRANCE
5	Institut Paoli-Calmettes - Marseille	Institut Paoli-Calmettes Hopital de jour 232 Boulevard Sainte Marguerite	13273	MARSEILLE	FRANCE
6	Johannes-Gutenberg-Universität Mainz	III. Medizinische Klinik und Poliklinik Bereich Hämatologie und Onkologie Langenbeckstr. 1	55131	Mainz	GERMANY
7	Krankenhaus Nordwest	II. Med. Klinik Onkologie - Hämatologie Steinbacher Hohl 2-26	60488	Frankfurt	GERMANY
8	LMU Klinikum der Universität München - Großhadern	Urologische Klinik und Poliklinik Marchioninistr. 15	81377	München	GERMANY
9	Medizinische Einrichtungen der Heinrich-Heine-Universität	Klinik für Hämatologie, Onkologie und klinische Immunologie Moorenstr. 5	40225	Düsseldorf	GERMANY
10	Universitätsklinikum Hamburg Eppendorf (UKE)	Klinik und Poliklinik für Urologie Martinistr. 52	20246	Hamburg	GERMANY

Appendix to Clinical Study Synopsis for study 11848

11	Universitätsklinikum Ulm	Urologische Universitätsklinik und Poliklinik Prittwitzstrasse 43	89075	Ulm	GERMANY
12	Akademia Medyczna	Klinika Onkologii, Oddzial Chemioterapii ul. Lakowa 1	61-878	Poznan	POLAND
13	Akademia Medyczna we Wroclawiu	Katedra i Klinika Urologii AM Pl. 1-go Maja 8	50-043	Wroclaw	POLAND
14	Centrum Onkologii - Instytut im. M.Sklodowskiej-Curie	Klinika Nowotworów Piersi i Chirurgii Rekonstrukcyjnej Centrum Onkologii ul. W.K. Roentgena 5	02-781	Warszawa	POLAND
15	SP Szpital Kliniczny nr 2 PAM	Klinika Urologii Al Powstancow Wielkopolskich 72	70-111	Szczecin	POLAND
16	Wojewodzkie Centrum Onkologii	ul. M. Sklodowskiej-Curie 2	80-210	Gdansk	POLAND
17	Wojskowy Instytut Medyczny	Klinika Onkologii - Oddzial Kobiecy Centralny Szpital Kliniczny WIM ul. Szaserow 128	04-141	Warszawa	POLAND
18	Clinical Oncology Dispensary	Sibirskiy tract, 29	420029	Kazan	RUSSIA
19	Hertzen Institute of Oncology	2nd Botkinsky pr. 3	125284	Moscow	RUSSIA

20	Russian Oncological Scientific Center n.a. N.N. Blokhin RAMS	Kashirskoe sh., 24	115478	Moscow	RUSSIA
21	City Oncology Hospital	Verhovinnaya str. 69	115	Kiev	UKRAINE
22	Donetsk Regional Oncological Center Regional Antitumor Cente	Polotskaya str. 2 a	83092	Donetsk	UKRAINE
23	Lvov Cancer Center	Gashek str. 2 a	79031	Lviv	UKRAINE
24	Royal Marsden Hospital (London)	Department of Medicine Fulham Road	SW3 6JJ	London	UNITED KINGDOM
25	Frederick Memorial Hospital	Regional Cancer Therapy Center 501 West Seventh Street	21701	Frederick	UNITED STATES
26	Nevada Cancer Institute	10000 West Charleston Boulevard	89135	Las Vegas	UNITED STATES
27	Oregon Health and Science University	Hematology Oncology Clinic 3303 SW Bond Avenue	97239	Portland	UNITED STATES
28	Texas Oncology, PA	Sammons Cancer Center 3535 Worth Street	75246	Dallas	UNITED STATES
29	The Cleveland Clinic	Taussig Cancer Institute 9500 Euclid Avenue	44195-0002	Cleveland	UNITED STATES
30	University of Colorado Hospital	UCCC Clinical Investigations Core 1665 North Ursula Street	80010	Aurora	UNITED STATES
31	Virginia Mason Medical Center	1100 Ninth Avenue	98101	Seattle	UNITED STATES

Product Identification Information

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

Date of last Update/Change: 28 Apr 2012