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.

Webposting Clinical Trial Results Synopsis

Study Sponsor:	Bayer Healthcare AG	
Study Number:	11538	NCT00492297
Study Phase:	II	
Study Title:	A Phase II, Multi-center, Open-label, Uncontrolled Study to Evaluate the Efficacy and Safety of BAY 43-9006 Given Daily in Combination with Repeated 21-Day Cycles of Dacarbazine (DTIC) Chemotherapy in Subjects with Advanced Metastatic Melanoma	
Therapeutic Area:	Oncology	
Name of Test Product:	Nexavar in combination with dacarbazine	
Active Ingredient:	BAY 43-9006/Sorafenib	
Dosage:	A 1-hour intravenous infusion of 1000 mg/m^2 dacarbazine was given to all subjects on Day 1, in combination with 21 days of oral BAY 43-9006 starting on Day 1. This cycle was repeated every 21 days. The dose of BAY 43-9006 was 400 mg twice a day, orally administered as 2 x 200 mg tablets. Dose modification due to toxicity was permitted.	
Reference Therapy:	Not applicable	
Dosage:		
Placebo:		
Route of Administration:		
Treatment Duration:	Subjects continued to receive combination therapy unless unacceptable toxicity or disease progression occurred. Subjects for whom it was medically appropriate to stop dacarbazine administration before progression was noted were permitted to continue to receive BAY 43-9006 as single agent therapy until disease progression was documented.	
Study Period:	Date of first subjects' first visit:	01 Apr 2005
	Date of last subjects' last visit	24 Jul 2008 (data cut-off)
Methodology:	This is a phase II, multi-center, open-label, uncontrolled study to evaluate the efficacy and safety profile of BAY 43-9006 administered in combination with dacarbazine chemotherapy in subjects with advanced metastatic melanoma. Although BAY 43-9006 was given continuously, the treatment period was split up into repeated 21-day cycles, with the dacarbazine infusion given on Day 1 of each cycle. Subjects continued to receive combination therapy, as long as it was having a clear palliative benefit and they were tolerating the combination treatment well, until progressive disease or death (if earlier) was recorded. Subjects for whom it was medically appropriate to stop dacarbazine administration were allowed to continue receiving BAY 43-9006 as single agent therapy until disease progression was documented or until transfer to an appropriate long term treatment program or commercial BAY 43-9006 supply, in which the subject could continue to receive single agent BAY 43-9006 (as per protocol Amendment 4). Baseline imaging examinations were performed within 28 days of the first dose of combination therapy and other screening assessments were conducted within 7 days of the first dose. All laboratory analyses were conducted at the investigative sites, with the exception of lipase analysis, which were performed centrally. Response evaluations were performed every 2 cycles for the first 8 cycles and every 4 cycles thereafter. An end-of-treatment assessment was to be performed as well. The responses identified by the investigators were reviewed by an independent radiology company. This secondary review was for regulatory purposes only.	
Study Site:	This was a multinational study. The study was conducted at 8 centers in the United Kingdom and 4 centers in France.	

Main Inclusion Criteria:	Subjects with advanced metastatic, histologically-confirmed melanoma, for whom treatment with dacarbazine was considered medically acceptable, were enrolled in this study. Subjects should have had measurable and evaluable disease (as per the RECIST criteria) and not have received prior cytotoxic chemotherapy. Prior immunotherapy, cytokine, or biological therapy was permitted, as long as there was at least 4 weeks recovery following the last dose of therapy prior to study entry. Prior vaccine therapy was also permitted, as long as there was at least 3 months recovery following the last administration of therapy prior to study entry (as per protocol Amendment 1). Subjects should also have had adequate bone marrow, hepatic and renal function, and normal pancreatic function.
Study Objectives:	Primary: • To evaluate the overall tumor response rate (Complete Responses +Partial Responses) of oral BAY 43-9006 given continuously in combination with repeated 21-day cycles of dacarbazine in subjects with advanced metastatic melanoma. The response rate was determined using the RECIST criteria. Secondary: • To evaluate progression-free survival in this subject population • To evaluate overall survival in this subject population [At Amendment 4, this objective was amended to further read: "at the cutoff date of 30th Nov 2007"; however, this cut-off date was not applied because the amendment approval was not granted until 2008.] • To evaluate duration of response in this subject population for those subjects who exhibit an objective response (Complete Response or Partial Response) • To evaluate the disease control rate (Complete Responses + Partial Responses + Stable Disease) in this subject population • To evaluate duration of Stable Disease in this subject population for those subjects who exhibit Stable Disease as their best response • To evaluate time to response in this subject population for those subjects who exhibit an objective response (either Complete Response or Partial Response) • To further evaluate the safety and toxicity profile of the combination study treatment in this subject population • To further explore possible BRAF mutations in melanoma biopsy samples that may correspond with a better response rate to the combination therapy of BAY 43-9006 and dacarbazine • To further analyze phosphorylated extracellular related kinase (p-ERK) and phosphorylated vascular endothelial growth factor receptor 2 (p-VEGFR-2) levels in melanoma biopsy samples to determine whether increased phosphorylation corresponds with a better response rate to the combination therapy of BAY 43-9006 and dacarbazine, and whether levels are modulated by the combination therapy. At Amendment 3, this objective was amended to further read: Other markers associated with these pathways may be analyzed.

Evaluation Criteria:	Efficacy (Primary): Efficacy: All subjects enrolled who received at least 1 dose of either study medication were considered evaluable for efficacy. Tumor response and disease progression were evaluated based on RECIST tumor response criteria. Measurements were made at baseline and then at the end of every 2 cycles (each cycle consisted of 21 days) during the treatment period, and also at the end-of-treatment visit if applicable. Subjects who continued to receive BAY 43-9006 after tumor assessment at the end of Cycle 8 were moved to a less frequent tumor assessment with scans at the end of every 4 cycles. The primary efficacy endpoint for this study was Best Overall Response of a subject, which was defined as the best tumor response that was achieved during or within 30 days after active therapy that was confirmed according to the RECIST tumor response criteria. The total number of Complete Responses (CR) and Partial Responses (PR) divided by the total number of subjects enrolled gave the Overall Response Rate. Efficacy (Secondary): Progression-free Survival was defined as the time from the first dose of combination study therapy to disease progression (radiological or clinical, whichever was earlier) or death (if death occurred before progression was documented). Progression-free survival for subjects without tumor progression or death at the time of analysis was censored at the date of last tumor evaluation. Overall Survival was measured from the date of starting study combination treatment until the date of death. As per Amendment 4, overall survival was evaluated until 30 Nov 2007, after which date, subjects in active follow-up or longterm follow-up were no longer to be evaluated; however, this cut-off date was not applied because the amendment approval was not received in all countries until January 2008. Duration of Response was assessed in those subjects who showed a Complete Response or Partial Response. It was defined as the time from the first documented objective response to disease progression, or death if before documented progression. Duration of response for subjects who had not progressed or died at the time of analysis was censored at the date of last tumor assessment. Overall Disease Control Rate was defined as the total number of subjects whose best response was not Progressive Disease (total number of Complete Responses + total number of Partial Responses + total number of Stable Diseases). The Disease Control Rate at specific time points could also be calculated as the total number of subjects whose response was not Progressive Disease at that time point (per Amendment 3). Duration of Stable Disease was assessed in those subjects who showed Stable Disease as best response. It was defined as the time from the first documented objective evidence of Stable Disease to disease progression, or death if before documented progression. Duration of Stable Disease for subjects who had not progressed or died at the time of analysis was censored at the date of last tumor assessment. Time to Response in subjects who achieved an objective response (Complete Response or Partial Response with confirmation) was measured from the date of starting study combination treatment until the earliest date that the response was first documented. Safety All subjects who received at least 1 dose of BAY 43-9006 or dacarbazine were considered evaluable for safety analysis. Treatment toxicity, including adverse events and some laboratory toxicities, were summarized by National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 3.0. Results of vital signs data (including heart rate, blood pressure, respiration rate and temperature), electrocardiogram data and weight were assessed. Pharmacokinetics Not applicable Biomarkers Analysis An analysis of biomarkers was performed and presented in the report appendices.

Statistical Methods:	This study was to use a 2-stage Simon optimal design consisting of 30 subjects in the first stage and 52 subjects in the second stage, giving a possible total of 82 subjects. If there were less than 6 responses (either complete or partial) in the first stage, the study was to end, with the conclusion that the combination treatment did not provide a greater response rate than dacarbazine alone. This would also be the conclusion if there were less than 18 responses from the overall total of 82 subjects. If there were 6 or more responses (either complete or partial) in the first 30 subjects and the total number of responses reached 18 within the total of 82 subjects, it would be concluded that there had been sufficient response to the combination treatment to warrant further evaluation. Again, this would also be the conclusion if there were 18 or more responses (either complete or partial) in the first 30 subjects. A total of 83 subjects received study medication. All subjects enrolled who received at least 1 dose of either study medication were considered evaluable for both efficacy and safety analyses. <u>Efficacy (Primary):</u> The overall best response of a subject was the best tumor response achieved during or within 30 days after active therapy that was confirmed by using unidimensional measurement according to RECIST tumor response criteria. The overall best response rates were calculated as the percentage of subjects with either a Complete Response or Partial Response from among the intent-to-treat (ITT) population evaluable for response and 95% confidence intervals (CI) were determined. <u>Efficacy (Secondary):</u> Disease Control Rate was based on the total number of subjects whose best response was not Progressive Disease (total number of Complete Responses + total number of Partial Responses + total number of Stable Diseases). The Disease Control Rate was calculated as the percentage of subjects with either a Complete Response or Partial Response or Stable Disease from among the ITT population evaluable for response and 95% CIs were determined. The Disease Control Rate at specific timepoints could also be calculated as the total number of subjects whose response was not Progressive Disease at that timepoint (Protocol Amendment 3). For overall survival (time to death), time to progression, duration of response, duration of Complete Response, duration of Partial Response, duration of Stable Disease and Progression-free Survival, summary statistics (N, median [Kaplan-Meier estimates], upper and lower quartiles, 95% CI, minimum and maximum) together with the total numbers of subjects censored and failed (that is, recording the event of interest) were determined. For time to response, the summary statistics N, median (Kaplan-Meier estimates), upper and lower quartiles, 95% CI, minimum and maximum were determined. The Eastern Cooperative Oncology Group Performance Status was summarized at baseline and for each cycle using frequency counts within each category. Percentages of subjects within each category were also presented based on numbers of subjects with non-missing information. <u>Safety</u> The display of adverse events presented tabulations by NCI CTC, version 3.0. Change in worst grade from baseline in adverse events was summarized using frequency counts and interval-specific and cumulative event rates for certain pre-specified adverse events and worst grades were also presented. Incidence rates of selected hematological and biochemical toxicities were presented by worst NCI CTC grade, together with change from baseline in grades (worst grade post-baseline by subject). Incidence rates of high and low hematology and biochemistry abnormalities (based on normal range) were also summarized. Summary statistics for vital signs and their change from baseline values were determined by cycle. Electrocardiogram interpretations by cycle and treatment-emergent incidence rates of electrocardiogram findings for Rhythm-conduction, P-Wave morphology and QRS-ST-T Wave complex together with percentages were determined and the incidence rates for treatment-emergent electrocardiogram findings were calculated. Summary statistics of electrocardiogram cardiac cycle measurements and their change from baseline were calculated by cycle. <u>Pharmacokinetics</u> Not applicable
Number of Subjects:	A total of 96 subjects were screened and 83 subjects were treated with study medication. Of the treated subjects, 50 were male and 33 were female. The mean age was 53.5 years (standard deviation [SD] 12.8 years). All enrolled subjects received dacarbazine plus BAY 43-9006.

Results Summary — Efficacy

The primary endpoint of this study was overall response rate, as determined by RECIST criteria and confirmed by independent review. Eighty-three subjects received study medication and of this ITT population, 75 subjects were evaluable for response. A total of 1 CR and 9 PRs were documented, for an overall best tumor response rate of 12.0% (95% CI 5.9% to 21.0%) in the ITT population Independent radiological review confirmed 9 responses. The median duration of response for the 10 subjects with best response of CR or PR was 327 days (46.7 weeks), including the duration of 420 days for the 1 subject who achieved a CR. In addition, another 31 (37.4%) subjects had an overall best response of Stable Disease. Median PFS was approximately 102 days, 14.6 weeks.

Results Summary — Pharmacokinetics

Not applicable

Results Summary — Safety

The toxicities of the dacarbazine/BAY 43-9006 combination were manageable in subjects with metastatic melanoma. The most common class of adverse events was associated with the gastrointestinal system, 44 subjects (53.0%) recording constipation, 43 (51.8%) with diarrhea and 38 (45.8%) with nausea, but in nearly all cases these were of Grade 1 or 2. The most common drug-related adverse events were associated with constitutional, dermatology/skin, gastrointestinal, and hematologic symptoms. Among the adverse events, only decreased neutrophils and platelets were reported as Grade 3 or 4 in more than 10% of the subjects. Most hematologic events and all of the reported Grade 3 or 4 decreased platelets were considered to be drug-related. There were 14 deaths during treatment or within 30 days of last dose of study drug. The causes of death were categorized as progressive disease (n=6), metastatic melanoma (n=1), hemorrhage (n=1), thrombosis (n=1), or missing (n=5). Of these, one death was attributed to treatment with study medication, hemorrhagic cerebrovascular accident. Intracerebral hemorrhage, is a known, though rare event, that is associated with treatment with BAY 43-9006 and is listed in the Investigator's Brochure.

All 83 subjects had at least 1 treatment-emergent adverse event of at least Grade 1, and 82 subjects (98.8%) had at least 1 drug-related treatment-emergent adverse event of at least Grade 1. Sixty-three subjects (75.9%) experienced Grade 3, 4, or 5 adverse events as their worst event. The incidence of Grade 3 or 4 hematologic adverse events reported in this study was higher than expected from other studies of dacarbazine or BAY 43-9006 alone. Grade 3 neutrophils were reported as an adverse event for 19.3% of the subjects, and Grade 4 neutrophils for 16.9% of the subjects. Grade 3 platelets were reported as an adverse event for 13.3% of the subjects and Grade 4 platelets for 8.4% of the subjects.

Except for the hematologic toxicities, hypophosphatemia, GGT, and lipase were the only biochemical toxicities reported as Grade 3 events in > 10% of subjects. Grade 3 hypophosphatemia was seen in 19.5% of subjects, which is similar to that reported in previous studies in other tumor indications. Grade 3 changes in GGT or lipase were observed in 15.4% (2/13) and 14.3% (4/28) of subjects, respectively; however, it should be noted that for these analyses only a subset of the study population provided samples.

Based on the safety results reported from this study, dacarbazine in combination with BAY 43-9006 was generally safe and well tolerated in subjects with metastatic melanoma. The adverse events were manageable with an acceptable safety profile.

Conclusion(s)

The results from the analysis of the 83 treated subjects are encouraging. In addition, toxicity with this regimen is manageable. This information will be added to the data from ongoing randomized studies testing BAY 43-9006 in combination with cytotoxic drugs for the treatment of metastatic melanoma.

Publication(s):

T Eisen et al: Sorafenib and dacarbazine as first-line therapy for advanced melanoma: phase I and open-label phase II studies. British Journal of Cancer (2011) 105, 353 – 359, 2011

Updated: 22 December 2011

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