Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: brivanib alaninate (BMS-582664)		
Name of Active Ingredient: brivanib		

SYNOPSIS

Abbreviated Clinical Study Report for Study CA182026: Ovarian Cancer

TITLE OF STUDY: A Randomized Discontinuation Study of Brivanib Alaninate (BMS-582664) Versus Placebo in Subjects with Advanced Tumors

INVESTIGATORS/STUDY CENTERS: There were 151 subjects with ovarian cancer enrolled at 16 investigational sites in the United States (US) (4 sites), Belgium (3 sites), Canada (2 sites), France (2 sites), the Netherlands (2 sites), United Kingdom (2 sites), and Poland (1 site).

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 06-Jul-2009 (ovarian cancer) **CLINICAL PHASE:** 2

Study Completion Date (database lock): 26-Mar-2012

OBJECTIVES:

Primary Objective:

- To compare progression-free survival (PFS) for brivanib alaninate versus placebo in subjects with advanced solid tumors with fibroblast growth factor-2 (FGF-2) over-expression and who have obtained stable disease (SD) after 12 weeks of treatment with brivanib alaninate.

Secondary Objectives:

- To determine the objective response rate (ORR), duration of response (DOR), time to response (TTR), disease stabilization rate (DSR), and change in tumor size in FGF-2 positive (+) subjects.
- To evaluate the safety of brivanib alaninate when given as monotherapy.
- To assess other biomarker studies and correlate with clinical outcomes: collagen IV, soluble vascular endothelial growth factor (sVEGF), vascular endothelial growth factor receptor (VEGFR-2), soluble FGF. This objective is not addressed in this report.
- To investigate associations between exposure to brivanib (BMS-540215) and changes in biomarkers. This objective is not addressed in this report.

METHODOLOGY:

This was a Phase 2 randomized discontinuation trial (RDT) to assess the efficacy and safety of 800-mg once daily (QD) brivanib alaninate with enrollment in subjects with non-small cell lung cancer, advanced soft tissue sarcoma, transitional cell carcinoma, gastric/esophageal adenocarcinoma, pancreatic cancer, breast cancer, and ovarian cancer. This report provides data on the ovarian cancer cohort only; data from the other cohorts are provided in separate reports. The RDT design in this study selects a population of subjects who experience disease stabilization on open-label active treatment prior to randomization.

The study was divided into the following 3 parts:

- **Open-label Lead-in Period:** This period was designed to determine which subjects were eligible for the randomized portion of the study. All eligible subjects began treatment with open-label brivanib alaninate (starting at 800 mg QD) for up to 12 weeks of treatment. Subjects with a complete response (CR) or partial response (PR) at Week 12 were assigned to open-label brivanib alaninate treatment. Subjects with progressive disease (PD) prior to or at the Week-12 assessments were discontinued and were not eligible for further treatment in this trial. Subjects with SD at Week 12 were eligible for randomization to either brivanib alaninate or placebo.
- **Randomized Period:** Subjects with SD at the end of the lead-in period were stratified by FGF-2 status and tumor type and randomized in a 1:1 ratio to either continue brivanib alaninate or placebo QD. In the randomized period, radiographic tumor assessments were performed every 6 weeks until Week 36, then every 12 weeks. Treatment unblinding was permitted when disease progression was documented during the randomized period.
- **Cross-over Period:** The cross-over period was an exploratory open-label period for randomized placebo subjects with documented disease progression who opted to continue on brivanib alaninate.

A study steering committee (SSC) was formed to help guide decision making on subject populations during the study. During the course of the study, the SSC reviewed accrual, FGF-2 expression frequency (blind was maintained), and tumor response to provide guidance to determine if enrollment in a given tumor type would continue or if cohorts enrolling subjects with other tumors would remain open.

NUMBER OF SUBJECTS (Planned and Analyzed):

Of the 151 subjects with ovarian cancer enrolled, 126 received treatment with brivanib alaninate in the lead-in period. Thirty-nine of the 126 treated subjects were randomized to either brivanib alaninate (n = 19) or placebo (n = 20) at the end of the lead-in period. Enrollment of subjects with ovarian cancer was closed by the sponsor at the recommendation of the SSC and in accord with protocol guidelines. The first subject in the ovarian cancer cohort was enrolled on 06-Jul-2009 and the last subject was enrolled on 22-Aug-2011.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Eligible subjects included females aged 18 or greater with ovarian cancer for which there was no approved effective therapy or who were intolerant of such therapy, and who had a life expectancy of at least 3 months, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Brivanib alaninate (200-mg tablets) was administered orally (PO) on a continuous daily starting dose of 800 mg until PD or unacceptable toxicity. Batch numbers of open-label brivanib alaninate were 0H52670, 8C38134, 8G34077, 9C51751, and 9H39469; batch numbers of brivanib alaninate used in the double-blind randomized period were 8C38134, 8G34077, and 9C54529.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Placebo was administered PO in the randomized period of the study. Batch numbers of placebo were 8C42410 and 8G40778.

CRITERIA FOR EVALUATION:

Efficacy Endpoints:

- The primary endpoint of this study was PFS during the double-blind, randomized period of the study for subjects who were FGF-2+.
- Secondary and exploratory efficacy endpoints of ORR, DOR, TTR, and DSR for all treated subjects and for FGF-2+ subjects (in the lead-in period and the randomized period), and of change in tumor size for all treated subjects (in the lead-in period) were assessed in this study.

Subjects were assessed for tumor response according to modified World Health Organization (mWHO) criteria.

Safety Endpoints: The safety and tolerability assessments of brivanib alaninate were secondary safety endpoints assessed for all treated subjects in this study. Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements and clinical laboratory tests.

STATISTICAL CONSIDERATIONS:

Discrete variables were summarized with the number and proportion of subjects falling into each category. Continuous variables were summarized with univariate statistics mean, median, minimum, maximum, Q1 to Q3, and standard deviation (SD). For time-to-event variables, Kaplan-Meier (K-M) curves were displayed. The graphs included the median with its corresponding confidence interval (CI), computed using the method of BrookMeyer and Crowley, and the number of subjects at risk at several time points. For the randomized portion, the hazard ratio (HR) from the Cox Proportional Hazards model with corresponding CI was presented.

Efficacy: Accrual in the ovarian cohort was interrupted earlier than the originally planned number of events (52) in the FGF-2 + group was reached; as a result, the statistical assumptions for the final analysis of PFS were modified. Based on the observations from the previously completed soft tissue sarcoma cohort that FGF-2+ status was not predictive of efficacy, the final analysis in the ovarian cancer cohort took place when approximately 28 events (progression or death) were observed in all randomized subjects (regardless of FGF-2 status) and the last randomized subject was followed for 2 months in the randomized period. This number of events was required to detect a HR of 0.33 corresponding to a median PFS of 4.2 months with brivanib alaninate compared to a median PFS of 1.4 months for placebo. Comparison of PFS in the randomized period between these 2 treatment groups was performed using a 2-sided, 5% level log-rank test with 80% power. Progression-free survival was defined per subject as the time from randomization date to the date of documented progression.

Safety: Incidence of deaths, AEs, drug-related AEs, serious adverse events (SAEs), drug-related SAEs, AEs of special interest (AEOSI), and AEs leading to discontinuation of therapy were tabulated. Drug-related AEs were those events with relationship to study therapy of certain, probable, possible, missing or unknown. All on-study AEs (reported on AE and SAE forms) were summarized for the entire treatment period from the first dosing date to the last dosing date plus 14 days for AEs, and from the first dosing date to the last dosing date plus 30 days for SAEs. On-study laboratory tests were defined as laboratory tests that were conducted after the start of treatment and no more than 14 days after the last dose of study therapy.

SUMMARY OF RESULTS:

Disposition of Subjects:

Of the 126 treated subjects in the lead-in period, 10 subjects continued on open-label brivanib alaninate (responders) and 39 were randomized to either brivanib alaninate or placebo (37 were dispensed randomized study medication, of which 36 took at least 1 dose of randomized treatment) (Table 1). Of the 39 randomized subjects, 37 had a tumor response of SD at Week 12 of the lead-in period and 2 had a tumor response of PR at Week 12 and were randomized in error. In addition, 14 subjects who were randomized to placebo crossed over to open-label brivanib alaninate after progression in the randomized period.

Table 1: Subject Disposition in CA182026 - Ovarian Cancer Cohort

	Number of Subjects
Enrolled	151
LEAD-IN PERIOD	
Total Treated	126
Discontinued Prior To Week 12	58[a]
Progressed Prior To Week 12 Assessment	37
Reached 12 Week Assessment	68[b]
Discontinued Treatment At Week 12	26
Continued On Open-label Treatment	10[c]
RANDOMIZED PERIOD	
Total Randomized	39
Randomized and Treated	36
Randomized To Brivanib Alaninate and Treated	17
Randomized To Placebo and Treated	19
Cross Over Period	
Entered Cross Over Period on Open-label Brivanib Alaninate	14

[a] Other than disease progression, the reasons for discontinuation from lead-in period prior to Week 12 included study drug toxicity (n = 12), AE unrelated to study drug (n = 5), withdrawal of consent (n = 3), and poor/non-compliance (n = 1).

[b] Included 12 subjects with best response in lead-in period of PR, 41 subjects with best response of SD, and 15 subjects with PD. In addition, 7 subjects with a Week 12 tumor response had a Week 12 status of 'not completed', including 5 subjects with a Week 12 response of PD and 2 subjects with a Week 12 response of SD.

[c] Subjects with a PR at the end of the lead-in period were eligible to continue open-label brivanib alaninate. Ten subjects remained on open-label treatment and 2 subjects were randomized in error.

Of the 126 treated subjects, 7 remained on study at the time of the database lock for this report (26-Mar-2012), including 1 subject (responder) who continued to receive open-label brivanib alaninate, 2 subjects who remained on study in the randomized period, and 4 subjects who remained on study in the cross-over period.

Demographic/Baseline Disease Characteristics:

Of the 126 treated subjects, most were white and < 65 years of age (Table 2). All but 2 subjects had an ECOG status of 0 or 1. For 1 subject, the pretreatment ECOG status was not reported and for the other, the pretreatment ECGO status was 2.

Table 2: Demographic Characteristics and Pretreatment Tumor Assessments (Index Disease) Summary: Ovarian Cancer - All Treated Subjects

	Total (N = 126)
Mean (SD) age, years	58.1 (10.56)
Gender, n (%) female	126 (100%)
Race, n (%) White	117 (92.9%)
Number of disease sites, n (%)	
1	46 (36.5%)
2	46 (36.5%)
≥3	34 (27.0%)
Median longest diameter of largest index lesion (mm) (range)	37 (10 - 134)

For 72 (57.1%) treated subjects, the initial pathological stage was metastatic disease and the most common disease sites for the index lesion were the lymph node (47.6%) and liver (32.5%). The majority of subjects had tumors of serous origin upon histology (69.8%). Subjects in the ovarian cancer cohort were heavily pretreated, with 76.2% having received 3 or more prior systemic chemotherapy regimens. Nineteen (15.1%) subjects received prior treatment with an anti-angiogenic agent, including 18 subjects who had received bevacizumab. Eighteen subjects (14.3%) had received prior radiotherapy.

Overall, 110 of the 126 treated subjects had a FGF status recorded on study. Ninety-seven subjects were FGF-2+ at baseline, including 36 of the 39 randomized subjects.

Extent of Exposure:

In the lead-in, open-label (responders), and randomized periods of the study, the median of the subject's mean daily dose was 638.8 mg, 592.9 mg, and 600 mg brivanib alaninate, respectively. The median duration of study therapy with brivanib alaninate was 2.6 months (95% CI: 2.4, 2.7), 3.0 months (95% CI: 2.1, 4.1), and 2.8 months (95% CI: 1.4, 4.1) for subjects in the lead-in, open-label (responders), and randomized periods of the study, respectively.

Efficacy Results:

At the time of the database lock date, a total of 31 PFS events had occurred during the randomized period (regardless of FGF-2 status). Most of the randomized subjects (36/39) were FGF-2+. The median PFS for randomized subjects who were FGF-2+ was 4.0 months in the brivanib alaninate group compared to 2.0 months in the placebo group. The hazard ratio of brivanib alaninate to placebo was 0.56 (95% CI: 0.26, 1.22), corresponding to a 44% reduction in the risk of disease progression with continued brivanib alaninate treatment compared to placebo (p = 0.1384, log-rank test). The PFS analysis for all randomized subjects regardless of FGF-2 status was consistent (hazard ratio of 0.54 [95% CI: 0.25, 1.17; p = 0.1124, log-rank test).

The secondary efficacy endpoints (DSR, ORR, TTR, DOR) were assessed for the FGF-2+ subjects during the open-label lead-in period (n = 97) and the randomized period (n = 36, respectively). Overall, brivanib alaninate 800 mg QD showed modest antitumor activity.

- Among FGF-2+ subjects treated with brivanib alaninate in the lead-in period, 8 subjects had a documented PR (ORR of 8.2% [95% CI: 3.6, 15.6]) and 37 subjects had SD (DSR of 38.1% [95% CI: 28.5%, 48.6%]).
- Among the 8 FGF-2+ responders in the lead-in period, the TTR ranged from 1.2 to 2.8 months and the DOR ranged from 1.4 to 9.9 months. No CR was observed on study.
- Among all randomized FGF-2+ subjects, 2 in the brivanib alaninate group and 1 in the placebo group achieved a PR during this period (ORR of 11.1% and 5.6%, respectively). Thirteen randomized FGF-2+ subjects (8 brivanib alaninate, 5 placebo) had a best tumor response of SD disease during the randomized period (DSR of 44.4% and 27.8%, respectively).

Safety Results:

The safety analysis included all brivanib alaninate treated subjects (n = 126) that received at least 1 dose during the study. Overall, treatment with brivanib alaninate, administered at 800 mg QD, was generally manageable in subjects with ovarian cancer.

- Ten deaths (7.9%) were reported during treatment or within 30 days of the last dose, all but one of which was attributed to disease progression by the investigator. The remaining death within 30 days of the last dose of study drug was attributed to study drug toxicity (intracranial hemorrhage).
- A total of 57 (45.2%) subjects experienced 1 or more SAEs, with 24 (19.0%) subjects having a drug-related SAE. The most common individual SAEs were malignant neoplasm progression (n = 8, 6.3%), ascites (n = 7, 5.6%), and vomiting (n = 4, 3.2%).
- Adverse events leading to discontinuation were reported for 33 (26.2%) treated subjects. A total of 16 (12.7%) subjects were discontinued due to drug-related AEs, of which ALT increased and AST increased were the most common (n = 3, 2.4% each).
- Slightly more than one-half of subjects had at least 1 dose reduction (52.4%) and/or 1 dose interruption (57.1%) while on study.
- All subjects reported an AE(s) on study (100%), and the most common AEs (> 25%, all grades) diarrhea (70.6%), fatigue (61.9%), nausea (54.3%), decreased appetite (45.2%), hypertension (39.7%), vomiting (38.9%), dizziness (38.1%), constipation (29.4%), ALT increased (27.8%), AST increased (27.0%), and abdominal pain (24.1%). A summary of AEs reported for > 5% of subjects is provided in Table 3.

Abnormalities in hematology or clinical chemistry laboratory parameters were commonly observed during the study; Grade 3 or 4 laboratory abnormalities occurring in more than 2 subjects on study were decreased ANC (5/122, 4.1%), hyponatremia (14/124, 11.3%) and hepatic function laboratory abnormalities of ALT (26/124, 21.0%), AST (18/124, 14.5%), and ALP (5/124, 5.0%). Increases in thyroid stimulating hormone (TSH) levels above the upper limit of normal (ULN) were reported for 62.4% (63/101) of treated subjects. The incidence of 1 on-study increase in TSH > ULN and 1 measurement of low triiodothyronine (T3) or thyroxine (T4), or free T3 and free T4 was 17.8% (18/101).

Table 3: Adverse Events > 5%- All Grades: Ovarian Cancer - All Treated Subjects

Treatment Group: Brivanib N=126

System Organ Class (%) Preferred Term (%)	Gr I, II, Unk	Gr III, IV,V	Total (Any Grade)
TOTAL SUBJECTS WITH AN EVENT	30 (23.8)	96 (76.2)	126(100.0)
ENDOCRINE DISORDERS	14 (11.1)	0	14 (11.1)
HYPOTHYROIDISM	14 (11.1)	0	14 (11.1)
GASTROINTESTINAL DISORDERS	77 (61.1)	39 (31.0)	116 (92.1)
DIARRHOEA	80 (63.5)	9 (7.1)	89 (70.6)
NAUSEA	64 (50.8)	5 (4.0)	69 (54.8)
VOMITING	44 (34.9)	5 (4.0)	49 (38.9)
ABDOMINAL PAIN	35 (27.8)	8 (6.3)	43 (34.1)
CONSTIPATION	34 (27.0)	3 (2.4)	37 (29.4)
STOMATITIS	19 (15.1)	1 (0.8)	20 (15.9)
DYSPEPSIA	17 (13.5)	0	17 (13.5)
ABDOMINAL PAIN UPPER	12 (9.5)	3 (2.4)	15 (11.9)
DRY MOUTH	14 (11.1)	0	14 (11.1)
ABDOMINAL DISTENSION	13 (10.3)	0	13 (10.3)
ASCITES	6 (4.8)	5 (4.0)	11 (8.7)
ABDOMINAL DISCOMFORT	7 (5.6)	0	7 (5.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	82 (65.1)	25 (19.8)	107 (84.9)
FATIGUE	63 (50.0)	15 (11.9)	78 (61.9)
MUCOSAL INFLAMMATION	21 (16.7)	0	21 (16.7)
ASTHENIA	10 (7.9)	9 (7.1)	19 (15.1)
OEDEMA PERIPHERAL	12 (9.5)	0	12 (9.5)
THIRST	12 (9.5)	0	12 (9.5)
PYREXIA	11 (8.7)	0	11 (8.7)
CHILLS	9 (7.1)	0	9 (7.1)
INFLUENZA LIKE ILLNESS	9 (7.1)	0	9 (7.1)
PAIN	5 (4.0)	2 (1.6)	7 (5.6)
INFECTIONS AND INFESTATIONS	21 (16.7)	6 (4.8)	27 (21.4)
URINARY TRACT INFECTION	9 (7.1)	2 (1.6)	11 (8.7)
INVESTIGATIONS	27 (21.4)	34 (27.0)	61 (48.4)
ALANINE AMINOTRANSFERASE INCREASED	10 (7.9)	25 (19.8)	35 (27.8)
ASPARTATE AMINOTRANSFERASE INCREASED	16 (12.7)	18 (14.3)	34 (27.0)
WEIGHT DECREASED	19 (15.1)	0	19 (15.1)
METABOLISM AND NUTRITION DISORDERS	43 (34.1)	23 (18.3)	66 (52.4)
DECREASED APPETITE	50 (39.7)	7 (5.6)	57 (45.2)
HYPONATRAEMIA	1 (0.8)	11 (8.7)	12 (9.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	57 (45.2)	3 (2.4)	60 (47.6)
BACK PAIN	22 (17.5)	2 (1.6)	24 (19.0)
MUSCLE SPASMS	13 (10.3)	0	13 (10.3)
PAIN IN EXTREMITY	11 (8.7)	0	11 (8.7)
MYALGIA	8 (6.3)	0	8 (6.3)
MUSCULOSKELETAL PAIN	7 (5.6)	0	7 (5.6)

Table 3: Adverse Events > 5%- All Grades: Ovarian Cancer - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Treatment Group: Brivanib N=126 Gr I, II, Unk	Gr III, IV,V	Total (Any Grade)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (3.2)	7 (5.6)	11 (8.7)
NEOPLASM MALIGNANT	4 (3.2)	4 (3.2)	8 (6.3)
NERVOUS SYSTEM DISORDERS	78 (61.9)	8 (6.3)	86 (68.3)
DIZZINESS	47 (37.3)	1 (0.8)	48 (38.1)
HEADACHE	32 (25.4)	2 (1.6)	34 (27.0)
SOMNOLENCE	12 (9.5)	0	12 (9.5)
LETHARGY	9 (7.1)	1 (0.8)	10 (7.9)
PERIPHERAL SENSORY NEUROPATHY	7 (5.6)	0	7 (5.6)
PSYCHIATRIC DISORDERS	22 (17.5)	2 (1.6)	24 (19.0)
ANXIETY	9 (7.1)	0	9 (7.1)
INSOMNIA	7 (5.6)	0	7 (5.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	48 (38.1)	8 (6.3)	56 (44.4)
DYSPHONIA	22 (17.5)	0	22 (17.5)
DYSPNOEA	17 (13.5)	4 (3.2)	21 (16.7)
COUGH	14 (11.1)	0	14 (11.1)
OROPHARYNGEAL PAIN	7 (5.6)	0	7 (5.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	43 (34.1)	3 (2.4)	46 (36.5)
RASH	12 (9.5)	0	12 (9.5)
DRY SKIN	9 (7.1)	0	9 (7.1)
PRURITUS	7 (5.6)	0	7 (5.6)
VASCULAR DISORDERS	46 (36.5)	10 (7.9)	56 (44.4)
HYPERTENSION	41 (32.5)	9 (7.1)	50 (39.7)

Includes AE with onset on or after the first dosing date and on or prior to the last dosing date +14 days or SAE with onset on or after the first dosing date and on or prior to the last dosing date +30 days
MedDRA Version: 14.1

CONCLUSIONS:

- The available data suggested that continued treatment with brivanib alaninate resulted in a non-significant PFS prolongation compared to treatment with placebo among subjects with ovarian cancer who had SD after 12 weeks of open-label treatment with brivanib alaninate.
  - The median PFS in FGF-2+ subjects randomized to continued brivanib was 4.0 months vs. 2.0 months in subjects randomized to placebo, yielding a hazard ratio of 0.56 (95% CI: 0.26, 1.22; p = 0.1384). Results were similar for all randomized subjects regardless of FGF-2 status.
- There was also suggestive evidence that brivanib alaninate at 800 mg QD demonstrated antitumor activity in a heavily pretreated population with ovarian cancer.
  - The ORR in FGF-2+ subjects was 8.2% at the end of the lead-in period with open-label brivanib alaninate. Three additional FGF-2+ subjects achieved a partial response during the randomized period (2 subjects randomized to brivanib and 1 subjects randomized to placebo).
  - For FGF-2+ subjects, the DSR was 38.1% at the end of the lead-in period with open-label brivanib alaninate (Week 12), and 44.4% for subjects randomized to brivanib alaninate and 27.8% for subjects randomized to placebo.

- Treatment with brivanib alaninate, administered at an initial dose of 800 mg QD, was generally manageable in subjects with ovarian cancer.
  - Slightly more than one-half of subjects had at least 1 dose reduction and/or 1 dose interruption on study.
  - One death occurring within 30 days of the last dose of study drug was attributed to study drug toxicity (intracranial hemorrhage).
  - Malignant neoplasm progression, ascites, and vomiting were the most common individual SAEs (each reported in more than 3 subjects).
  - ALT increased and AST increased were the only individual drug-related AEs that led to discontinuation of more than 2 subjects.
  - The most commonly reported Grade 3 to 5 AEs (> 5%) were ALT increased, AST increased, hyponatremia, asthenia, hypertension, diarrhea, abdominal pain, and decreased appetite.
  - Liver function elevations, decreased hemoglobin, and low sodium measurements were the most commonly recorded laboratory abnormalities.

DATE OF REPORT: 21-Sep-2012