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DASATINIB

Final Clinical Study Report for Study CA180088

Phase 2 Study of Dasatinib (BMS-354825) for Advanced Estrogen/Progesterone Receptor-Positive or HER2/NEU-Positive Breast Cancer

Indication:	Advanced Estrogen/Progesterone Receptor-positive or HER2/NEU-positive Breast Cancer
Phase:	2
Study Initiation Date:	20-Dec-2006
Study Completion Date:	06-May-2009
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
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Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: SPRYCEL		
Name of Active Ingredient: Dasatinib		

SYNOPSIS

Final Clinical Study Report for Study CA180088

TITLE OF STUDY: Phase 2 Study of Dasatinib (BMS-354825) for Advanced Estrogen/Progesterone Receptor-Positive or HER2/Neu-Positive Breast Cancer

INVESTIGATORS/STUDY CENTERS: Ninety-two subjects were enrolled at 24 sites in the United States, Spain, Belgium, France, Argentina, Italy, and Peru.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 20-Dec-2006 (First Subject First Visit) **CLINICAL PHASE:** 2

Study Completion Date: 06-May-2009 (Last Subject Last Observation)

OBJECTIVES: The primary objective was to estimate, by subgroup, the objective response rate (ORR) of dasatinib in women with recurrent or progressive locally advanced or metastatic breast cancer.

The secondary objectives included 1) To estimate, by subgroup, the disease control rate (DCR) and proportion free of progression at Weeks 9, 17, and 25; progression-free survival (PFS) distribution; and response duration, 2) To determine the safety and tolerability of dasatinib in this population, 3) To obtain pharmacokinetic (PK) and pharmacodynamic data, and 4) To obtain exploratory tumor biomarker and pharmacogenomic data.

METHODOLOGY: This was a prospective open-label, 2-stage, Phase 2 trial of dasatinib. Subjects were classified by tumor type at study entry into 1 of 2 subgroups:

- Group A: Her2/neu–amplified, defined as 3+ by immunohistochemistry (IHC) or positive by fluorescent or chromogenic in situ hybridization (FISH or CISH), regardless of estrogen receptor (ER)/progesterone receptor (PgR) status.
- Group B: ER and/or PgR positive, defined as > 10% of cells positive by IHC (unless Her2/neu–amplified).

Dasatinib was administered initially at 100 mg twice daily (BID) for a total daily dose (TDD) of 200 mg, and decreased by protocol amendment to 70 mg BID, for a TDD of 140 mg, in subsequent subjects. Study assessments were performed every 2 weeks for the first 2 months, every 4 weeks for 2 visits (after 3 and 4 months on treatment) and every 8 weeks thereafter. The primary analysis was performed when all

on-treatment subjects had been observed for a minimum of 24 weeks or had discontinued treatment, and corresponding data had been received at Bristol-Myers Squibb (BMS).

Documentation of partial response (PR) in the second treated subject in Group A and the second treated subject in Group B satisfied the protocol-defined criterion for continued accrual.

NUMBER OF SUBJECTS (Planned and Analyzed): Ninety response-evaluable subjects were planned. A total of 92 subjects were enrolled and 70 subjects were treated (24 in Group A and 46 in Group B). Sixty-nine of the 70 treated subjects were considered response evaluable (24 in Group A and 45 in Group B).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Female subjects with measurable recurrent or progressive breast cancer who had received anthracycline- and/or taxane-containing chemotherapy (at any time) and not more than 2 chemotherapy regimens in the metastatic setting were studied.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Dasatinib was administered initially at 100 mg BID and decreased by protocol amendment to 70 mg BID in subsequent subjects. Subjects continued to receive study drug as long as tolerated until progressive disease.

Dasatinib 20 mg tablet	Dasatinib 50 mg tablet
5E01532; 5E01543; 5E01546; 5E01547	5H01127/5G4302Z; 5K09694/5J4324Z; 5K09695/5J4325Z

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Not applicable

CRITERIA FOR EVALUATION:

Efficacy: The ORR was the primary study endpoint. Secondary efficacy measures included DCR, duration of objective response, and PFS.

Safety: Assessment of safety was based on medical review of adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), echocardiograms, physical examination results, and vital signs. Eastern Cooperative Oncology Group (ECOG) performance status was also evaluated.

Pharmacokinetics: Pharmacokinetic assessment was initially required but became optional by amendment. If performed, blood samples for plasma dasatinib concentrations were collected pre-dose, and 1, 3, and 6 hours after dosing at the Week 3 visit (Day 15 ± 4 days) and repeated at either the Week 7 or Week 9 visit, as clinically convenient. An additional trough sample was obtained immediately prior to any dose approximately 12 hours after last dose, as convenient.

Pharmacodynamics: Assays of vascular endothelial growth factor receptor -2 (VEGFR2) and collagen type IV in plasma, obtained at baseline and after 2 and 4 weeks of treatment, were performed by enzyme linked immunosorbent assay (ELISA).

STATISTICAL CONSIDERATIONS: A Gehan 2-stage design was used in this study. In the first stage, 29 response-evaluable subjects were accrued. If no responses were observed, the study would have been closed to accrual with the conclusion that the true response rate was unlikely (95% confidence) to be ≥10%. Otherwise, if there was at least 1 response, 16 additional response-evaluable subjects would be accrued in the second stage. Groups A and B were considered independently for both accrual and efficacy.

The ORR was defined as the proportion of response-evaluable subjects with complete response (CR) or PR as the best response recorded during study. The ORR was summarized using frequency tables with 95%

exact confidence interval (CI). DCR was defined as the proportion of response-evaluable subjects with CR or PR as best response or with stable disease (SD) recorded at or after 16 weeks of study. The DCR and corresponding 95% exact CI were reported.

Duration of response was defined as the time between the first date that criteria for CR or PR were met until the first date that progressive disease was observed, and was analyzed for response-evaluable subjects who achieved a CR or PR. Subjects who died without reported progressive disease were considered to have progressive disease on the date of death. Subjects who neither progressed nor died were censored at the date of last tumor evaluation.

On-study AEs were graded in severity by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0 grading system. For each AE, the causal relationship to dasatinib was determined by the investigator (certain, probable, possible, not likely, or unrelated). The investigator AE terms were coded and grouped by system organ class using MedDRA, version 11.

Means and standard deviations were tabulated for dasatinib plasma concentrations by starting dose (100 mg BID and 70 mg BID) and timepoint (Week 3 and Week 7/9). Summary statistics were provided for VEGFR2 and Collagen Type IV and reported as percent change from baseline by time point and by dose.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: Subject disposition is presented in Table 1. The age of the study population ranged from 32 to 70 years and 46 (66%) subjects were ≥ 50 years. Most subjects were white (91%). Baseline and demographic characteristics are presented in Table 2.

Table 1: Subject Disposition

	Group A	Group B	Overall
No. of Subjects Treated	24	46	70
No of Response-evaluable subjects	24	45	69
No. of Subjects Discontinued	24	46	70
Disease Progression	21	35	56
Study Drug Toxicity	1	7	8
AE Unrelated to Study Drug	1	2	3
Subject Request	1	1	2
Subject Withdrew Consent	0	1	1

Table 2: Baseline and Demographic Characteristics

	Group A (N = 24)	Group B (N = 46)	Overall (N = 70)
Age			
Mean (years)	52.2	54.3	53.6
Min, Max (years)	32, 68	33, 70	32, 70
Age Categorization N (%)			
< 50 years	8 (33.3)	16 (34.8)	24 (34.3)
≥ 50 years	16 (66.7)	30 (65.2)	46 (65.7)

Table 2: Baseline and Demographic Characteristics

	Group A (N = 24)	Group B (N = 46)	Overall (N = 70)
Race N (%)			
White	21 (87.5)	43 (93.5)	64 (91.4)
Black/African-American	2 (8.3)	0	2 (2.9)
American Indian/Alaska Native	0	2 (4.3)	2 (2.9)
Other	1 (4.2)	1 (2.2)	2 (2.9)

Efficacy Results: Results of the primary efficacy analysis are presented in Table 3.

Table 3: Results of BMS Assessment of Best Response

	Group A (N = 24)	Group B (N = 45)	Overall (N = 69)
Best Overall Response [N (%)]			
Unconfirmed Partial Response	0	1 (2.2)	1 (1.4)
Partial Response	1 (4.2)	2 (4.4)	3 (4.3)
Stable Disease	4 (16.7)	8 (17.8)	12 (17.4)
Progressive Disease	16 (66.7)	22 (48.9)	38 (55.1)
Clinical Progression	1 (4.2)	4 (8.9)	5 (7.2)
Discontinuation Due to Study Drug Toxicity	2 (8.3)	7 (15.6)	9 (13.0)
No Reassessment	0	1 (2.2)	1 (1.4)
Objective Response Rate [N (%)]	1 (4.17)	2 (4.44)	3 (4.35)
95% Confidence Interval	(0.11, 21.12)	(0.54, 15.15)	(0.91, 12.18)

The subjects with objective responses were:

- One subject, who was the second treated subject in Group B and initially received dasatinib 100 mg BID, had a confirmed PR with a duration of 18.14 weeks and disease progression at Week 42.
- One subject, who was the second treated subject in Group A and initially received dasatinib 100 mg BID, had a confirmed PR with a duration of 31.14 weeks and disease progression at Week 38. This subject's tumor was also ER positive.
- One subject, who was in Group B and initially received dasatinib 70 mg BID, had a confirmed PR with a duration of 8.29 weeks and discontinued for toxicity at Week 45.

As assessed by BMS, a total of 9 subjects had disease control, including the 3 subjects with confirmed PR, one subject with uPR, and 5 subjects with SD ≥16 weeks. (The remaining 7 subjects with a BOR of SD had a duration <16 weeks). When summarized by group, the 9 subjects included the 3 subjects with confirmed PR plus 1 additional subject in Group A whose tumor was also ER positive and 5 additional subjects in Group B. The DCR was 13.0% overall, 8.3% in Group A and 15.6% in Group B.

In the BMS assessment of PFS, 61 of the 70 treated subjects progressed or died. The median PFS was 8.1 weeks (95% CI: 7.7 – 8.3) for all subjects as well as for subjects in Group A and in Group B. The probabilities (SE) of PFS at 9, 17, and 25 weeks were 0.32 (0.06), 0.18 (0.05), and 0.08 (0.03), respectively and were similar for Group A and Group B.

Investigator assessments of primary and secondary efficacy variables were generally consistent with those observed by BMS.

Safety Results: A summary of safety is presented in Table 4. The most common (>25% at either dose) drug-related AEs of special interest were pleural effusion, diarrhea, headache, nausea, fatigue, abdominal pain, asthenia, rash, dyspnea, and vomiting. Most events were mild to moderate; 5 subjects had severe (Grade 3 or 4) fatigue and 4 subjects had severe asthenia.

Ten of the 12 deaths were due to disease progression. Among the 13 subjects who reported drug-related SAEs, 3 of the 6 subjects who initially received dasatinib 100 mg BID had Grade 3 events: pleural effusion, dehydration, fluid retention, diarrhea, nausea, and vomiting. No Grade 4 events were reported in these subjects. Two of the 7 subjects with drug-related SAEs who were initially treated with 70 mg BID had Grade 3 events (abdominal pain and fatigue) and 1 subject had a Grade 4 pulmonary embolism. Among the 16 subjects who discontinued due to AEs of any relationship or grade, only 1 event was reported per category except for pleural effusion (5 subjects), asthenia (4 subjects), fatigue (2 subjects), health deterioration (2 subjects), and dyspnea (2 subjects).

Most clinical laboratory abnormalities were mild to moderate; granulocyte, asparatate amniotransferase (AST), and phosphorus were the only Grade 3 abnormalities reported in more than 1 subject. Clinically significant changes from baseline echocardiograms were noted for 5 subjects, 3 of whom initially received dasatinib 100 mg BID and 2 of whom initially received dasatinib 70 mg BID.

No occurrences of QTc prolongation were reported as AEs. Five subjects had clinically significant echocardiogram abnormalities, including diastolic left ventricular dysfunction with and without changes in ejection fraction, pericardial and pleural effusions, and an increase in ejection fraction. Clinically significant changes in vital signs and physical examinations were reported as AEs. Fourteen subjects had a worsening in ECOG performance status.

Table 4: Overall Summary of Safety

	Number (%) of Subjects	
	Dasatinib 100 mg BID* N = 23	**Dasatinib 70 mg BID** N = 47**
All Deaths	6 (26)	6 (26)
Drug-related SAEs	6 (26)	7 (15)
AEs Leading to Discontinuation	5 (22)	11 (23)
All AEs	23 (100.0)	47 (100.0)
Drug-related AEs	22 (96)	44 (94)
Drug-related Grade 3 AEs	9 (39)	15 (32)
Notable Drug-related AEs		
Diarrhea	10 (44)	22 (47)
Nausea	8 (35)	16 (34)
Abdominal Pain	2 (9)	11 (23)
Fatigue	3 (13)	17 (36)

Table 4: Overall Summary of Safety

	Number (%) of Subjects	
	Dasatinib 100 mg BID* N = 23	**Dasatinib 70 mg BID** N = 47**
Rash	8 (35)	11 (23)
Pleural Effusion	9 (39)	12 (26)
Dyspnea	9 (39)	10 (21)
On-study Grade 3-4 Laboratory Abnormalities		
Granulocytes	1 (4.3)	1 (2.1)
Hemoglobin	0	1 (2.1)
Platelet Count	0	1 (2.1)
Partial Thromboplastin Time	1 (4.3)	0
Alkaline Phosphatase	0	1(2.1)
Alanine Aminotransferase	0	1 (2.1)
Aspartate Aminotransferase	1 (4.3)	3 (6.4)
Creatinine	1 (4.3)	0
Hypokalemia	1 (4.3)	0
Hyponatremia	0	1 (2.1)
Phosphorus	2 (8.7)	1 (2.1)
Bilirubin	0	1 (2.1)

*200 mg TDD; **140 mg TDD

Pharmacokinetic Results: At 1, 3 and 6 hours postdose, the mean plasma concentration was at the maximum at 1 hour for all doses and timepoints. The mean (standard deviation [SD]) plasma concentrations for subjects initially treated with dasatinib 100 mg BID at 1 hour were 107.1 (64.6) and 131.1 (57.5) ng/mL for Week 3 (N = 16) and Week 7/9 (N = 5), respectively. Similarly, mean (standard deviation [SD]) plasma concentrations for subjects initially treated with dasatinib 70 mg BID at 1 hour were 77.2 (61.9) and 49.3 (38.0) ng/mL for Week 3 (N = 14) and Week 7/9 (N = 8), respectively. The mean trough concentrations were 9.5 - 10.8 ng/mL for subjects initially treated with dasatinib 100 mg BID and 6.6 - 7.0 ng/mL for subjects initially treated with dasatinib 70 mg BID.

Pharmacodynamic Results: Increased circulating levels of Collagen IV and VEGFR2 from baseline were observed at Weeks 3 and 5 in both treatment groups.

CONCLUSIONS:

- Despite substantial pre-clinical rationale, the activity of single-agent dasatinib in advanced Her2-amplified or ER/PgR-positive breast cancer was limited:
  - The ORR was 4.2% in Group A, 4.4% in Group B, and 4.4% overall
  - The DCR was 8.3% in Group A, 15.6% in Group B, and 13.0% overall
  - The proportion of subjects free of progression at Week 17 was 14% in Group A, 20% in Group B, and 18% overall.
  - Median PFS was 8.1 weeks in both groups
  - All 9 subjects with clinical benefit had ER- and/or PgR-positive tumors
- Based on Grade 3 drug-related AEs as well as interruptions and dose reductions resulting in sub-optimal dose intensity in subjects initially treated at 100 mg BID, dasatinib at an initial dose of 70 mg BID was better tolerated in this patient population. Lower doses may be considered for patients less tolerant of side effects.
- As limited activity was detected in this study, use of single-agent dasatinib is not recommended for further study in advanced breast cancer. Combinations of dasatinib with other therapies may be explored.

DATE OF REPORT: 13-Oct-2009