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:		

SYNOPSIS

Final Clinical Study Report for Study CA180059

TITLE OF STUDY: Phase 2 Study of Dasatinib (BMS-354825) for Advanced 'Triple-Negative' Breast Cancer

INVESTIGATORS/STUDY CENTERS: Fifteen investigators enrolled subjects at 15 sites worldwide in US, France, Italy, Spain, and Belgium

PUBLICATIONS: Finn RS, Bengala C, Ibrahim N, Strauss LC, Fairchild J, Sy O, Roché H, Sparano J, and Goldstein LJ. Phase II Trial of Dasatinib in Triple-negative Breast Cancer: Results of Study CA180059. Cancer Res 69 (Suppl):242s [abstract #3118]. Presented at 31st San Antonio Breast Cancer Symposium December, 2008.

STUDY PERIOD: Study Initiation Date: **CLINICAL PHASE:** Phase 2
First Subject First Visit: 19-Dec-2006

Study Completion Date:
Last Subject Last Observation: 9-Sep-2008

OBJECTIVES: The primary objective was to estimate objective response rate (ORR) of dasatinib in women with recurrent or progressive locally-advanced or metastatic 'triple-negative' breast cancer.

Secondary objectives included: 1) To estimate Disease Control Rate (DCR) and proportion free of progression at Week 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 open-label 2-stage Phase 2 study of dasatinib. 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. Subjects were evaluated at least every 2 weeks ±4 days for the first 8 weeks (Weeks 3, 5, 7, 9), every 4 weeks for 2 visits (after 3 and 4 months on treatment), and every 8 weeks ± 1 week thereafter. The primary analysis was performed when all on-treatment subjects were observed for a minimum of 24 weeks or discontinued treatment. Subjects continued to receive study drug as long as tolerated until progressive disease.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 55 subjects were enrolled over the course of the study. Forty-four subjects were treated. In the first stage, 29 subjects were treated. The 15th subject treated had partial response (PR) observed at the first on-study assessment, which was subsequently confirmed. Therefore, the design criterion for opening the second stage was satisfied. In the second stage, 15 subjects were treated. Out of 44 treated subjects, 43 were response evaluable.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Female patients with measurable recurrent or progressive breast cancer, which is 'triple-negative' (ie, negative for estrogen receptor [ER], progesterone receptor [PgR] and Her2/neu), were studied. Invasive breast cancer was based on previous biopsy, documented as negative for expression of ER and PgR [< 10% of cells stained] and for Her2/neu [IHC 0-1+ *or* CISH/FISH-negative]. Only women of child-bearing potential (WOCBP) were included and was defined as any female who had experienced menarche and who had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or was not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL].

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 5E01547	5H01127/5G4302Z 5K09694/5J4324Z

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

CRITERIA FOR EVALUATION:

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

Safety: Assessment of safety was based on medical review of adverse events (AEs), clinical laboratory tests, and electrocardiograms (ECGs). 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. The investigator AE terms were coded and grouped by preferred term and system organ class using Medical Dictionary for Regulatory Affairs (MedDRA), version 11, and were summarized by any grade, Grade 3 to 4, and Grade 5.

Pharmacokinetics: Pharmacokinetic assessment was optional. Plasma dasatinib concentrations for nominal time points (0, 1, 3, 6, and 12 hours) were calculated by dose (70 mg and 100 mg BID) and treatment (week 3 and week 7/9).

Pharmacodynamics: Assays of 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 two-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.

ORR was defined as proportion of Response-evaluable subjects with complete response (CR) or PR as best response recorded during study. ORR was summarized using frequency tables along with its 95% exact confidence interval (CI). DCR was defined as proportion of Response-evaluable subjects with CR or PR as best response or with stable disease (SD) at or after 16 weeks on study recorded during study. DCR was reported, along with its 95% exact CI.

Duration of response was defined as time between the first date that criteria for CR or PR were met until the first date that progressive disease was observed, and were 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. Duration of response was analyzed, a Kaplan-Meier curve and a 95% CI about the median duration were produced.

The categories and definitions of severity used for AEs are defined in the NCI CTCAE, version 3.0. 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 by dose (70 mg BID and 100 mg BID) and treatment (Week 3 and Week 7/9) for dasatinib PK parameters at various time points. 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: A total of 55 subjects were enrolled and of these, 44 were treated. Subject disposition is presented in Table 1. The age of the study population ranged from 29 to 71 years and 31 (70.5%) subjects were ≥ 50 years. Most subjects were white (89%). Baseline and demographic characteristics are presented in Table 2.

Table 1: Subject Disposition

	100 mg BID	70 mg BID	Overall
No. of Subjects Treated	23	21	44
No. of Response-evaluable Subjects	23	20	43
No. of Subjects Discontinued	23	21	44
Disease Progression	13	13	26
Study Drug Toxicity	3	5	8
Subject Request	5	0	5
Other	2	0	2
Adverse Event Unrelated to Study Drug	0	1	1
Lost to Follow-up	0	1	1
Subject Withdrew Consent	0	1	1

Table 2: Demographic Characteristics; All Treated

	100 mg BID	70 mg BID	Overall
Age			
Mean (years)	56.4	51.5	54.0
Min, Max (years)	39, 71	29, 67	29, 71
Age Categorization N (%)			
< 50 years	4 (17.4)	9 (42.9)	13 (29.5)
≥ 50 years	19 (82.6)	12 (57.1)	31 (70.5)
Gender N (%)			
Female	23 (100.0)	21 (100.0)	44 (100.0)
Race N (%)			
White	20 (87.0)	19 (90.5)	39 (88.6)
Black/African American	2 (8.7)	1 (4.8)	3 (6.8)
Asian	0	1 (4.8)	1 (2.3)
Other	1 (4.3)	0	1 (2.3)

Efficacy Results: In the total population of 43 response-evaluable subjects, 2 confirmed partial responses (both in the 100 mg BID group) were observed, for an ORR of 4.7% (Table 3). The DCR was 9.3% (4/43). In the 70 mg BID group, none of the subjects achieved CR or PR. Per BMS assessment, 30 of the 44 treated subjects progressed or died (Figure 7.2.1A). Of these 30 subjects, 29 progressed and 1 died. The median PFS was 8.3 weeks (95% CI: 7.3 - 15.3).

Table 3: BMS Response Rates - Response Evaluable Subjects

	Number (%) of Subject		
	100 mg BID N = 23	**70 mg BID N = 20**	**Overall N = 43**
BEST OVERALL RESPONSE			
UNCONFIRMED COMPLETE RESPONSE	0	0	0
COMPLETE RESPONSE	0	0	0
UNCONFIRMED PARTIAL RESPONSE	0	0	0
PARTIAL RESPONSE	2 (9)	0	2 (5)
STABLE DISEASE	7 (30)	5 (25)**	12 (28)**
PROGRESSIVE DISEASE	10 (44)	12 (60)	22 (51)
CLINICAL PROGRESSION	0	0	0
DISCONTINUATION DUE TO TOXICITY	4 (17)	3 (15)	7 (16)
OBJECTIVE RESPONSE RATE (ORR)	2 (9)	0	2 (5)
95% CONFIDENCE LIMITS	(1.07, 28.04)		(0.57, 15.81)
DISEASE CONTROL RATE (DCR)	3 (13)	1 (5)	4 (9)
95% CONFIDENCE LIMITS	(2.78, 33.59)	(0.13, 24.87)	(2.59, 22.14)

**Subject [redacted] (70 mg BID): Reported best response of "SD" should be "PD" based on post database lock correction.

Safety Results: A summary of safety is presented in Table 4. All subjects reported at least 1 AE, any relationship and any grade. The most common (> 25%) drug-related AEs were nausea, fatigue, diarrhea, rash, dyspnea, pleural effusion, anorexia, headache, cough, abdominal pain, vomiting, and flushing. No Grade 4 drug-related events were reported. Most events were mild to moderate. A total of 7 deaths were reported of which 5 were due to disease progression**.** Fourteen (32%) subjects reported serious AEs (SAEs), any relationship and any grade. One subject reported a drug-related SAE in the 70 mg BID group compared with 5 subjects in the 100 mg BID group.

With the exception of Grade 3 neutropenia in 3 subjects, all hematology abnormalities were mild to moderate. On-study Grade 3 or 4 abnormalities in ALT, AST, and ALP were uncommon.

Table 4: Safety Summary for Treated Patients

	Number (%) of Subjects	
	100 mg BID N = 23	**70 mg BID N = 21**
All AEs	23 (100)	21 (100)
Drug-related AEs	23 (100)	19 (91)
Drug-related Grade 3 AEs	12 (52)	8 (38)
Notable Drug-related AEs		
Nausea	10 (44)	14 (67)
Fatigue	10 (44)	14 (67)
Rash	11 (48)	5 (24)
Pleural Effusion	9 (39)	7 (33)

Table 4: Safety Summary for Treated Patients

	Number (%) of Subjects	
	100 mg BID N = 23	**70 mg BID N = 21**
Dyspnea	11 (48)	6 (29)
Drug-related SAEs	5 (22)	1 (5)
Drug-related AEs Leading to Discontinuation	4 (17)	6 (29)
All Deaths	5 (22)	2 (10)
Grade 3/4 Laboratory Abnormalities		
Neutropenia	3 (13)	0
Hypocalcemia	0	1 (5)
Hypokalemia	1 (4)	0
Hypophosphatemia	1 (4)	2 (10)

Pharmacokinetic Results: Out of 1, 3, and 6 hour time points, mean plasma concentration was maximum at 1 hour for all doses and treatments. The plasma concentration values of dasatinib were within the range of concentration values obtained in other solid tumor or leukemia patients at the same dasatinib dose regimens.

Pharmacodynamic Results: Increased circulating levels of Collagen IV and VEGFR2 from baseline were observed at weeks 3 and 5, with somewhat greater increase in Collagen Type IV than for VEGFR2.

CONCLUSIONS:

- Despite substantial preclinical rationale and in vitro data, the clinical efficacy of single agent dasatinib in advanced triple-negative breast cancer was limited: ORR of 4.7% (2/43) with DCR of 9.3% (4/43)
- Based on interruptions and dose reductions, with overall incidence of Grade 3 drug-related AEs of 38%, dasatinib at 70 mg BID was considered a maximum-tolerated dose in this patient population

DATE OF REPORT: 11-Feb-2009