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 CA180274

ABBREVIATED REPORT

TITLE OF STUDY: Randomized Phase II of CCNU Versus CCNU + dasatinib in Patients With Recurrent Glioblastoma

INVESTIGATORS/STUDY CENTERS: 28 subjects were enrolled at 5 sites in Europe: 1 in France (4 subjects), 1 in Italy (9 subjects), 2 in Netherlands (9 subjects), and 1 in Switzerland (6 subjects).

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 20-Oct-2009 **CLINICAL PHASE:** II

Study Completion Date: 31-Mar-2011

INTRODUCTION: This study was an exploratory trial, performed in close collaboration with the Brain Tumor Group of the European Organization for Research and Treatment of Cancer (EORTC), to investigate the combination of dasatinib with CCNU (lomustine) in patients with recurrent glioblastoma (GBM). The study was designed to integrate a non-randomized safety cohort of at least 10 patients ("run-in" phase) aimed at documenting the safety profile and recommended dose of dasatinib when added to standard CCNU, followed by a randomized Phase 2 which was to address the overall therapeutic strategy on combining dasatinib and CCNU or CCNU alone. However, recruitment to the safety "lead-in" phase was halted when the review of safety and laboratory data from this safety "lead-in" phase indicated that administration of dasatinib in combination with CCNU was limited, also requiring reduction of the CCNU dose. Thrombocytopenia was the major dose-limiting toxicity (DLT) encountered. Accordingly, the randomized Phase 2 phase of the study was not performed. This abbreviated clinical study report provides a summary of demography, disposition and safety data on all subjects treated in the safety "lead-in" phase conducted at five sites. In addition, limited assessments of efficacy endpoints are also included.

OBJECTIVES: The general objectives of this study were to assess the safety of add-on dasatinib to standard of care (CCNU) as well as to assess the activity of this add-on therapy in GBM patients who have relapsed after standard therapy with temozolomide and radiotherapy. The primary end-point of the safety "lead-in" phase was the safety and tolerance of dasatinib+CCNU combination in order to establish a recommended dose for the Phase 2 part. A complete list of objectives are provided in the protocol.

METHODOLOGY: For the first 3 patients, cycle 1 was given with dasatinib at the dose of 100 mg QD and escalated to 100 mg BID in cycle 2.

- In the absence of DLTs in the first 3 patients, the 7 subsequent patients were to be treated at 100 mg BID.
- In case of 1 DLT, 3 additional patients were to be included. If this DLT occurred at cycle 1 (lead-in 100mg QD) then these 3 patients were to start with lead-in dose of 100mg QD. If no DLT was observed in these 3 last patients, the 4 subsequent patients were to be included starting at 100mg BID dose level.
- In case of 2 DLTs in up to 6 patients, an intermediate dose was to be explored.

The recommended dose was defined as the dose of dasatinib which did not lead to DLTs in more than 2 patients out of 10.

Patients included in the safety phase were to remain on study until one of the withdrawal criteria occurred (see Section 5.5 of the protocol). Dose-limiting toxicities were to be documented over the first 2 cycles for patients starting with dasatinib at 100 mg QD and further escalated to dasatinib 100 mg BID and on cycle 1 for patients starting upfront with dasatinib 100 mg BID. The duration for observation of DLT was therefore 2 cycles in patients with escalated dose and 1 cycle for patient starting with BID regimen.

Patients were considered assessable for the safety phase, if they completed the period for DLT observation. Patients dropping the study for any reason other than toxicity during the DLT documentation /observation period were to be replaced. Intermediate dose level of dasatinib 150 mg administered as 100 mg am and 50 mg pm could be explored if needed. No higher dose level was to be explored.

Dose-limiting toxicities were defined as adverse drug reactions as follows:

- absolute neutrophil counts (ANC) less than 0.5×10^9/L (grade 4) lasting for 7 consecutive days
- febrile neutropenia (neutrophil count less than 1×10^9/L and fever of at least 38.5°C)
- thrombocytopenia grade 4 (according to CTCAE v3.0)
- any Grade 3-4 non hematological toxicity (according to CTCAE v3.0) except nausea, vomiting and fever which could be rapidly controlled with appropriate measures
- any toxicity which did not allow administering at least 70% of the intended dose intensity for both agents

NUMBER OF SUBJECTS (Planned and Analyzed): A nonrandomized safety phase of a minimum of 10 subjects was planned to be analyzed prior to randomization. A total of 28 subjects were enrolled, and 26 started allocated dose level. Data cutoff date was 15-Sep-2011.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects ≥ 18 years of age with (i) histological or cytological proven glioblastoma multiforme, including anaplastic oligoastrocytoma with necrosis, (ii) recurrent or progressive disease (PD) documented by magnetic resonance imaging (MRI) after prior therapy [standard radiotherapy with concomitant and adjuvant temozolomide (TMZ)] within 2 weeks prior to registration/randomization, (iii) may be operated for recurrence; if operated, residual and measurable disease after surgery was not required but surgery must have confirmed the recurrence, (iv) at least one bidimensionally measurable target lesion for non-operated patients, and (v) no prior chemotherapy for recurrent disease.

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

For the first 3 patients of the safety cohort, Cycle 1 was given with dasatinib at the dose of 100 mg QD and escalated to 100 mg BID in Cycle 2. The daily oral intake of dasanitib was to take place at approximately the same time each day. One cycle was defined as 6 weeks for both dasatinib and CCNU combination. In the absence of DLTs in the first 3 patients, the 7 subsequent patients were to be treated at 100 mg BID. In case of 1 DLT, 3 additional patients were to be included. If this DLT occurred at Cycle 1 (lead-in 100mg QD) then these 3 patients were to start with lead-in dose of 100mg QD. If no DLT was observed in these

3 patients, the 4 subsequent patients were to be included starting at 100mg BID dose level. In case of 2 DLTs in up to 6 patients, an intermediate dose was to be explored.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT: CCNU 110 mg/m^2 was administered orally on Day 1 and repeated every 6 weeks. The body surface area was kept at 2.0 M^2 maximum.

CRITERIA FOR EVALUATION:

Safety: Safety information was collected for all treated subjects. Adverse events considered by the investigator as not drug related (i.e. reported as unrelated) were not considered as side effects or toxicity. Hematological toxicity was assessed on the basis of blood counts. The nadir count was computed for each cycle of therapy, and graded according to the CTCAE version 3.0. Non hematological acute adverse events were assessed and reported separately for each cycle of therapy, and graded according to the CTCAE version 3.0. Any study drug toxicity was assessed continuously. Subjects with study drug related toxicities were followed continuously during treatment and every 30 days off treatment until all study drug related toxicities resolved (or ≤ CTCAE grade 1), stabilized, returned to baseline or were deemed irreversible.

DLT and MTD criteria: DLTs were defined as adverse drug reactions as described in the methodology above. DLTs were documented in the first 2 cycles for patients with escalated dose and in Cycle 1 for patients starting upfront with dasatinib 100 mg BID. The MTD and recommended dose were defined as the dose of dasatinib which did not lead to DLTs in more than 2 patients out of 10.

Efficacy: Response to treatment was assessed on the basis of a set of target lesion(s) chosen before the first treatment administration (the complete list of target lesions was reported on the initial measurement form before the start of treatment). These lesions were initially measured in their two perpendicular dimensions, and these measurements were repeated at each evaluation of the disease by the same method. Response evaluation was based on neuro-radiological imaging (MRI). To avoid difficulties with response measurement, only patients with clearly enhancing tumors with at least the largest diameter at entry equal or superior to 2 cm were eligible (with the exception of re-resected patients). The contrast enhancing area was considered as the basis for the tumor size assessment. Tumor size was defined as the product of the two largest perpendicular diameters. Only reductions in cross-sectional areas of 50% or more were considered true responses. When calculating the response, the baseline scan was used for comparison. In responding or stabilized patients, new scans were compared to the scan showing the maximum response (= minimum tumor size) during/after treatment. In most patients, only one lesion was expected to be present. In case of multifocal disease, a maximum of 3 lesions were chosen as target. All lesions other than target lesions, if applicable, were assessed according to the same schedule. They were only taken into account in two situations:

- if one of them clearly progressed, the overall response to therapy was evaluated as "progression", independent of the response of target lesions
- all lesions had completely disappeared to report a "complete response"

Adequate investigations were carried out at each evaluation of the disease to detect eventual new lesions. If any new lesion was found, the response was evaluated as "progression".

STATISTICAL CONSIDERATIONS: The safety cohort was an open label, non-randomized, multicenter trial. As the combination of dasatinib plus CCNU had not previously been studied, a non-randomized safety phase of minimum 10 subjects was planned for analysis prior to the randomized Phase II part.

DLTs were documented over the first 2 cycles for patients starting with dasatinib at 100 mg QD and further escalated to dasatinib 100 mg BID and on cycle 1 for patients starting upfront with dasatinib 100 mg BID. The duration for observation of DLT was therefore 2 cycles in patients with escalated dose and 1 cycle for patient starting with BID regime. For patients receiving dasatinib at 150mg, DLTs were only documented over cycle 1.

Enrolled population: This is defined as "all enrolled patients, whether treated or not".

Safety population: This is defined as "all enrolled patients who have been treated".

Evaluable patient population: This is the subset of patients that was used to decide on the dose escalations. Patients were assessable, if they completed the period for DLT observation. Patients dropping the study for any other reason than toxicity during the DLT documentation /observation period had to be replaced.

All baseline characteristics and exposure to treatment are displayed in the safety population.

Tables on safety present the adverse events and laboratory tests pertaining to the DLT assessment period in the safety population. The tables of worst grade of toxicity report the worst grades of adverse events and laboratory tests observed during all cycles are displayed in the safety population. The table which summarizes DLTs is displayed in the evaluable population. Safety analyses included the frequency of assessment of AEs, serious adverse events (SAEs), deaths, AEs leading to discontinuation, and laboratory abnormalities.

The activity of the treatment and further anticancer therapy analyses are performed in the safety population. Efficacy data are limited, based on a small non-randomized population, and therefore should be interpreted with caution.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Table 1: Subject Disposition

	DL 1A (N=7)	**DL 1B (N=3)**	**DL 2 (N=7)**	**DL 3A (N=10)**	**DL 3B (N=1)**	**Overall (N=28)**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
No. of Subjects Enrolled	7 (100.0)	3 (100.0)	7 (100.0)	10 (100.0)	1 (100.0)	28 (100.0)
No. of Subjects Treated	6 (85.7)	3 (100.0)	7 (100.0)	9 (90.0)	1 (100.0)	26 (92.9)
No. of Treated Subjects Discontinued	6 (100.0)	3 (100.0)	7 (100.0)	9 (100.0)	1 (100.0)	26 (100.0)
Progression of disease/ Relapse / Death	3 (50.0)	3 (100.0)	7 (100.0)	8 (88.9)	1 (100.0)	22 (84.6)
Thrombocytopenia Gr 4	2 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	3 (11.5)
Both progression and toxicity	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)

DL 1A: Dasatinib:100mg QD/100mg BID - CCNU: 110 mg/m²; **DL 1B**: Dasatinib:100mg QD/100mg BID - CCNU: 90 mg/m²; **DL 2**: Dasatinib:100mg BID - CCNU: 90 mg/m²; **DL 3A**:Dasatinib:150mg/day (100 mg AM and 50 mg PM) - BID - CCNU: 90 mg/m²; **DL 3B**: Dasatinib:100mg/day - CCNU: 90 mg/m²

Table 2: Demographics and Selected Baseline Characteristics, by Dose Level: All Treated Subjects

	DL 1A (N=6)	DL 1B (N=3)	DL 2 (N=7)	DL 3A (N=9)	DL 3B (N=1)	Overall (N=26)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sex						
male	5 (83.3)	3 (100.0)	5 (71.4)	6 (66.7)	1 (100.0)	20 (76.9)
female	1 (16.7)	0 (0.0)	2 (28.6)	3 (33.3)	0 (0.0)	6 (23.1)
Age						
Median	58.8	57.7	53.6	49.7	51.1	54.8
Range	41.3 - 70.7	48.9 - 57.7	42.4 - 64.0	38.8 - 66.8	51.1 - 51.1	38.8 - 70.7
Histological diagnosis of primary disease (by local pathologist)						
glioblastoma multiforme	6 (100.0)	2 (66.7)	5 (71.4)	8 (88.9)	1 (100.0)	22 (84.6)
glioblastoma with oligodendroglial component	0 (0.0)	1 (33.3)	2 (28.6)	1 (11.1)	0 (0.0)	4 (15.4)
Performance status						
0	6 (100.0)	2 (66.7)	1 (14.3)	4 (44.4)	1 (100.0)	14 (53.8)
1	0 (0.0)	1 (33.3)	5 (71.4)	4 (44.4)	0 (0.0)	10 (38.5)
2	0 (0.0)	0 (0.0)	1 (14.3)	1 (11.1)	0 (0.0)	2 (7.7)

Safety Results: An overview of safety data for all treated subjects is provided in Table 3.

Table 3: Overview of Safety - All Treated Subjects

	DL1A	DL1B	DL2	DL3A	DL3B	Total
	N = 6	N = 3	N = 7	N = 9	N = 1	N = 26
Number of Deaths within 30 Days of Tx Discontinuation (n, %)	1* (16.7)	0 (0.0)	1* (4.3)	0 (0.0)	0 (0.0)	2 (7.7)
Number of Treatment-Related Deaths within 30 Days of Tx Discontinuation (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Subjects With At Least 1 SAE (n, %)	5 (83.3)	1 (33.3)	4 (57.1)	4 (44.4)	0 (0.0)	14 (53.8)
Number of Subjects With At Least 1 Treatment-related SAE (n, %)**	4 (66.7)	0 (0.0)	1 (4.3)	1 (11.1)	0 (0.0)	6 (23.1)
Number of Subjects Discontinuing Due to AEs (n, %)	3 (50.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	4 (15.4)
Gr 4 Thrombocytopenia (all considered treatment related)	2 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	3 (11.5)
Gr 3 Thrombocytopenia (considered treatment related) and PD	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Number of Subjects With At Least 1 AE (n, %)	6 (100.0)	3 (100.0)	7 (100.0)	9 (100.0)	1 (100.0)	26 (100.0)
Number of Subjects With At Least 1 Grade 3/4 AE (n, %)	2 (33.3)	2 (66.7)	4 (57.1)	4 (44.4)	0 (0.0)	12 (46.2)
Number of Subjects With At Least 1 Treatment-related AE (n, %)	5 (83.3)	2 (66.7)	5 (71.4)	7 (77.8)	1 (100.0)	20 (76.9)
Number of Subjects With At Least 1 Treatment-related Grade 3/4 AE (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Subjects With DLTs based on the evaluable population; N=23 (n, %)	3/5 (60.0)	0 (0.0)	3/5 (60.0)	4/9 (44.4)	0 (0.0)	10/23 (43.5)
Grade 4 Thrombocytopenia	2	0	1	3	0	6
Dasatinib interrupted for Grade 3 thrombocytopenia and/or dose reduced for Grade 2 thrombocytopenia leading to RDI <70%.	1	0	2	1	0	4

* Note: Pt [redacted] and Pt [redacted], for both cases the cause of death was progressive disease.

** Calculated manually.

Other Results - Response to Treatment:

Best overall response was assessed in all 26 patients who received at least one dose of study medication. The best overall response was partial response (PR) in 1 patient (dose level 1B; dasatinib:100mg QD/100mg BID - CCNU: 90 mg/m²), stable disease (SD) in 6 patients [4 at dose level 1A (dasatinib:100mg QD/100mg BID - CCNU: 90 mg/m²), 1 each at dose level 2 (dasatinib:100mg BID - CCNU: 90 mg/m²) and dose level 3A (dasatinib:150mg/day (100 mg AM and 50 mg PM) BID - CCNU: 90 mg/m²)].

Progression Free Survival (PFS): All 26 patients who received at least one dose of study medication had progressed at the time of data cutoff date (15-Sep-2011) for this report. The median progression-free survival (95% CI) was 1.35 months (1.22, 1.38).

Overall Survival (OS): Fifteen (15) of the 26 patients (57.7%) who received at least one dose of study medication had died by the time of data cutoff date (15-Sep-2011) for this report. The median overall survival (95% CI) was 6.37 months (3.78, 10.15).

Other Results - Pharmacokinetics of Dasatinib: There was no difference in the C_{max}, T_{max}, AUC_{inf} and half-life of dasatinib on Day 1 and Day 8 of Cycle 1.

CONCLUSIONS: The combination of dasatinib + CCNU was not well-tolerated, requiring both reduction of CCNU dose and limitation of dasatinib exposure to levels below those planned. In addition, there was no evidence of a treatment effect in this population. The lead-in phase was completed; however the tolerable doses were below those expected to provide sufficient efficacy and thus the study did not proceed to the randomized phase.

DATE OF REPORT: 08-Nov-2011.