SYNOPSIS

Final Clinical Study Report for Study CA198002

TITLE OF STUDY: A Phase 1/2 Multiple Ascending Dose Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of BMS-863233 in Subjects with Advanced and/or Metastatic Solid Tumors

PURPOSE: This study was designed to explore multiple dosing of BMS-863233, a Cdc7 serine-threonine kinase inhibitor in humans. This study was to evaluate the safety profile, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of BMS-863233 administered once daily on Days 1 to 14 of a 28-day cycle. This study was planned to consist of 2 phases, Phase 1 to determine the maximum tolerated dose (MTD) in subjects with advanced and/or metastatic solid tumors and a Phase 2 to provide a preliminary assessment of the anti-tumor activity of BMS-863233 in subjects with advanced and/or metastatic colorectal, breast carcinomas, bone/soft tissue sarcomas whose tumors demonstrated Cdc7 pathway activation.

The study was terminated due to (i) the presence of a metabolite that accumulated to exposures that achieved or surpassed levels of the parent drug and, (ii) the identification of an at risk population that had a poor metabolizer (PM) phenotype, leading to accumulation of the parent drug at very high levels and (iii) the identification of CYP1A2 as an enzyme that is involved in the metabolism of the parent compound. Because the CYP1A2 enzyme has considerable genotypic and phenotypic polymorphism necessitating a complex screening program, which would have been necessary for further clinical development and it was deemed that such a program would not be practical or manageable. In addition, preliminary clinical data from this study indicated that BMS-863233: (iv) appeared to have a potential signal for QTcB prolongation, (v) had an unexpectedly short half life, (vi) appeared to lack any clinical efficacy, and (vii) had a moderate to high inter-subject PK variability.

NUMBER OF SUBJECTS:

Phase 1: Thirty (30) subjects were planned; 15 subjects were enrolled of which 11 subjects were treated.

Phase 2: Fifteen (15) subjects were planned; however, the Phase 2 of the study was not started due to termination of the study.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

A total of 11 subjects were treated. All subjects discontinued treatment for various reasons. The reasons for discontinuing treatment included: disease progression (9 subjects, 81.8%), AE unrelated to study drug (1 subject, 9.1%) and study drug toxicity (1 subject, 9.1%). A summary of subject disposition of all treated subjects is presented in table below:

Subject Disposition: All treated subjects

	BMS-863233			Total
	25 mg	50 mg	100 mg	
Treated, n	**3**	**3**	**5**	**11**
Subjects not completing the study, n [a] (%)	3 (100)	3 (100)	5 (100)	11 (100)
Reason for not completing the study treatment, n (%)				
Disease progression	3 (100)	3 (100)	3 (60)	9 (81.8)
Study drug toxicity	0 (0)	0 (0)	1 (20)	1 (9.1)
Adverse event [b]	0 (0)	0 (0)	1 (20)	1 (9.1)

[a] Subjects not completing the study is defined as treatment discontinuation by the subject due to either disease progression, unacceptable toxicity, or per the subject's request.

[b] Adverse event summarized here are those not related to study medication.

Of the 11 treated subjects, 6 (54.5%) were male and 5 (45.5%) were female with a mean age of 60 years (range: 46-73 years). Subject ethnicities were as follows: 81.8%white caucasian and 18.2% others. A summary of baseline demographic characteristics for all treated subjects is given in table below.

Baseline Demographic Characteristics: All treated subjects

	BMS-863233			Total (N=11)
	25 mg (N=3)	50 mg (N=3)	100 mg (N=5)	
Age (years)				
Mean (SD)	56.0 (14.8)	61.0 (13.1)	61.8 (7.6)	60.0 (10.3)
Min-Max	47-73	46-70	53-70	46-73
Age Categorization				
<65	2 (66.7)	1 (33.3)	3 (60)	6 (54.5)
>=65	1 (33.3)	2 (66.7)	2 (40)	5 (45.5)
Gender				
Male, n (%)	1 (33.3)	2 (66.7)	3 (60.0)	6 (54.5)
Female, n (%)	2 (66.7)	1 (33.3)	2 (40.0)	5 (45.5)
Race				
White	2 (66.7)	2 (66.7)	5 (100)	9 (81.8)
Other	1 (33.3)	1 (33.3)	0	2 (18.2)

SD: Standard deviation, Min: minimum, Max: maximum

SUMMARY OF SAFETY RESULTS:

- Overall, there were 3 deaths reported in the study; 2 (18.2%) deaths occurred within 30 days of the last dose of study medication and 1 (9.1%) death occurred at 160 days after the last dose of study medication in subjects treated with BMS-863233.

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- Serious adverse events (SAEs) were reported in 6 (54.5%) subjects treated with BMS-863233. Drug related SAEs were reported in 2 (18.2%) subjects treated with 100 mg BMS-863233. No drug related SAEs were reported in subjects treated with 25 mg BMS-863233 and 50 mg BMS-863233.
- AEs leading to discontinuation were reported in 2 (18.2%) subjects treated with BMS-863233.
- All subjects experienced at least one AE during the study. Drug-related AEs were reported in 5 (45.5%) subjects.
- One (9.1%) of the 11 BMS-863233 treated subjects experienced a dose limiting toxicity (DLT).
- Marked laboratory abnormalities (Grade 3 - 4) included: low haemoglobin, low platelet count, low lymphocyte count, low white blood cell count (WBC), low neutrophil count, low hyponatremia, low inorganic phosphorus, and high alanine aminotransferase (ALT) .

Overall Safety Summary: All treated subjects

	BMS-863233			**Total (N=11)**
	25 mg (N=3)	**50 mg (N=3)**	**100 mg (N=5)**	
Deaths, n (%)	0 (0)	1 (33.3)	2 (40)	3 (27.3)
At least one AE, n (%)				
Any Grade	3 (100)	3 (100)	5 (100)	11 (100)
Grade 3-4	1 (33.3)	1 (33.3)	2 (40)	4 (36.4)
Grade 5	0 (0)	0 (0)	2 (40)	2 (18.2)
At least one related AE, n (%)				
Any Grade	1 (33.3)	0 (0)	4 (80)	5 (45.5)
Grade 3-4	0 (0)	0 (0)	2 (40)	2 (18.2)
At least one SAE, n (%)				
Any Grade	1 (33.3)	1 (33.3)	4 (80)	6 (54.5)
Grade 3-4	1 (33.3)	1 (33.3)	2 (40)	4 (36.4)
Grade 5	0 (0)	0 (0)	2 (40)	2 (18.2)
At least one related SAE, n (%)				
Any Grade	0 (0)	0 (0)	2 (40)	2 (18.2)
Grade 3-4	0 (0)	0 (0)	2 (40)	2 (18.2)

Overall Safety Summary: All treated subjects

	BMS-863233			Total (N=11)
	25 mg (N=3)	50 mg (N=3)	100 mg (N=5)	
AE leading to discontinuation, n (%)				
Any Grade	0 (0)	0 (0)	2 (40)	2 (18.2)
Grade 3-4	0 (0)	0 (0)	2 (40)	2 (18.2)

DATE OF REPORT: 09-Mar-2011