SYNOPSIS

Final Clinical Study Report for Study CA190002

TITLE OF STUDY: A Phase 1/2, Ascending Multiple-Dose Study to Evaluate the Safety, Efficacy and Pharmacokinetics of BMS-753493 in Subjects with Advanced Cancer.

PURPOSE: The purpose of this study was to evaluate the safety profile, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of BMS-753493 in subjects with advanced cancer. The investigational drug, BMS-753493, a folate conjugate of an epothilone analog BMS-748285, was designed to target folate receptor (FR) expressing tumor cells. This study was planned to consist of two phases. Phase 1 was an open-label, dose-escalation study of BMS-753493 administered as a 3 to 5 minute intravenous (i.v) infusion on Days 1 through 4 of a 21-day cycle in subjects with advanced cancer. Phase 2 was planned to assess the efficacy of BMS-753493 in subjects with advanced ovarian, renal or breast cancer. The Phase 2 portion of the study was not completed as the epothilone folate program was terminated due to lack of a clear efficacy signal among the treated subjects. A synoptic format was chosen for this report.

NUMBER OF SUBJECTS: Forty subjects were planned for Phase 1 of the study, 30 subjects were treated. Sixty five subjects were planned for Phase 2 of the study, 9 subjects were treated. All subjects completed the study.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Subject Disposition: - All Treated Subjects

	BMS-753493 (mg)						Total
	2.5 (N=3)	5 (N=3)	8 (N=3)	12 (N=5)	15[a] (N=21)	17 (N=4)	(N=39)
Treated and Completed, n (%)	3 (100)	3 (100)	3 (100)	5 (100)	21 (100)	4 (100)	39 (100)
Off treatment, n (%)	3 (100)	3 (100)	3 (100)	5 (100)	21 (100)	4 (100)	39 (100)
Reason for Off Treatment, n (%)							
Disease progression	3(100)	2 (67)	1 (33)	4 (80)	14 (67)	3 (75)	27 (69)
Adverse event unrelated to study drug	0 (0)	0 (0)	1 (33)	1 (20)	2 (10)	0(0)	4 (10)
Study drug toxicity	0 (0)	1 (33)	0 (0)	0 (0)	3 (14)	0(0)	4 (10)
Subject request to discontinue	0 (0)	0 (0)	0 (0)	0 (0)	2 (10)	1(25)	3 (8)
Others[b]	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0(0)	1 (3)

[a] A total of 21 subjects were enrolled in 15 mg group of which 9 subjects entered the phase II.

[b] "Others" include lost to follow up and subject no longer meets study criteria

Pretreatment Subject Characteristics: All Treated Subjects

	BMS-753493 (mg)						Total
	2.5 (N=3)	5 (N=3)	8 (N=3)	12 (N=5)	15 (N=21)	17 (N=4)	(N=39)
Age, (yr)							
Mean (SD)	54 (5)	59 (7)	55 (8)	52 (16)	57(12)	56 (8)	56 (11)
Min, Max	50, 59	53, 66	47, 62	29, 69	27, 76	46, 64	27, 76
Gender, n (%)							
Male	1 (33)	3 (100)	1 (33)	2 (40)	6 (29)	1 (25)	14 (36)
Female	2 (67)	0 (0)	2 (67)	3 (60)	15 (71)	3 (75)	25 (64)
Race, n (%)							
White	3 (100)	3 (100)	3 (100)	4 (80)	20 (95)	4 (100)	37 (95)
Asian	0	0	0	1 (20)	1 (5)	0	2 (5)
Not Reported	0	0	0	0	0	0	0
Ethnicity, n (%)							
Not Hispanic/Latino	3 (100)	1 (33)	1 (33)	1 (20)	10 (48)	2 (50)	18 (46)
Not reported	0 (0)	2 (67)	2 (67)	4 (80)	11 (52)	2 (50)	21(54)

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

SUMMARY OF SAFETY RESULTS:

Overall Safety Summary: All Treated Subjects

	BMS-753493 (mg)						Total
	2.5 (N=3)	5 (N=3)	8 (N=3)	12 (N=5)	15 (N=21)	17 (N=4)	(N=39)
Deaths, n (%)							
Overall	1 (33)	1 (33)	2 (67)	3(60)	7 (33)	1 (25)	15 (39)
Cause of death							
Disease progression	1(33)	1(33)	1(33)	3(60)	5 (24)	1(25)	14 (36)
Other reasons	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	1 (5)
At least one AE, n (%)							
Any grade	3(100)	3(100)	3(100)	5(100)	21(100)	4(100)	39(100)
Grade 3	1 (33)	1 (33)	2 (67)	2(40)	12 (57)	3(75)	21 (54)
Grade 4	0 (0)	1 (33)	0 (0)	0(0)	2 (10)	0 (0)	3 (8)
Grade 5[a]	0 (0)	0 (0)	0 (0)	1 (20)	1 (5)	1 (25)	3 (8)
At least one SAE, n (%)							
Any grade	0 (0)	2 (67)	2 (67)	2 (40)	11 (52)	3 (75)	20 (51)
Grade 3	0 (0)	1(33)	2(67)	1 (20)	9 (50)	2 (50)	15 (39)
Grade 4	0(0)	1(33)	0 (0)	0 (0)	1 (5)	0 (0)	2 (5)
Grade 5[a]	0 (0)	0 (0)	0 (0)	1 (20)	1 (5)	1 (25)	3 (8)
AE leading to discontinuation, n (%)							
Any grade	0 (0)	1 (33)	2 (67)	1 (20)	7 (33)	0 (0)	11 (28)
Grade 3	0 (0)	0 (0)	1 (33)	0 (0)	5 (24)	0 (0)	6 (15)
Grade 4	0(0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	1 (3)

[a] Includes one Grade 5 AE of Stevens-Johnson Syndrome at 15 mg, and two AEs of malignant neoplasm progression.

Overall, death was reported in 39% (15 subjects) of subjects treated with BMS-753493 of which 36% (14 subjects) died due to disease progression. One subject died due to the event of Steven Johnson Syndrome.

The overall proportion of subjects with at least one serious adverse event (SAE) in subjects treated with BMS-753493 was 51% (20 subjects). Three SAEs (fatigue, nausea and anorexia) in a subject treated with 17 mg BMS-753493 were considered by the investigator to be possibly related, 1 SAE (hypersensitivity) in a subject treated with 15 mg BMS-753493 was considered to be probably related, and 1 SAE (Steven-Johnson syndrome) in a subject treated with 15 mg BMS-753493 was considered to be certainly related, to the study medication.

The overall proportion of subjects with an adverse event (AE) leading to discontinuation in subjects treated with BMS-753493 was 28% (11 subjects) which included AEs unrelated to study drug in 7 subjects and study drug toxicity in 4 subjects. All subjects experienced at least one AE during the study.

All study subjects went off treatment; the reasons for going off treatment include disease progression in 27 subjects, study drug toxicity in 4 subjects, AEs unrelated to study drug in 4 subjects, a request for discontinuation in 3 subjects, and other reasons in 1 subject.

Of the eleven (11) subjects who had AE leading to discontinuation, end of treatment status included disease progression in 3 subjects, AEs unrelated to study drug in 4 subjects, and study drug toxicity in 4 subjects.

Three of the 39 subjects experienced dose limiting toxicities (DLTs), which included 2 subjects (Grade 3 ALT increased in one subject; Grade 3 nausea and Grade 3 fatigue in other subject) treated with 17 mg BMS-753493 and one subject (Grade 3 fatigue) treated with 15 mg BMS-753493. The maximum tolerated dose (MTD) was determined to be 15 mg, and 9 subjects were treated at this dose in the Phase 2 portion of the study. The recommended phase 2 dose was not determined due to early termination of the program.

Marked laboratory abnormalities (Grade 3 - 4) included low haemoglobin, low lymphocyte, low white blood cell count (WBC), low neutrophil count, hyponatremia, hypocalcemia, low phosphorus, elevated alanine transaminase, elevated aspartate transaminase, and elevated alkaline phosphatase. A marked laboratory abnormality was only reported as adverse events when the treating investigator found the abnormality to be clinically significant.

Events of clinical interest included transaminitis, fluid retention characterized by peripheral oedema with or without ascites, pleural or pericardial effusions, neuropathy, mucosal inflammation, rash and hypersensitivity. Program-wide, rash was associated with lacrimation and stomatitis in some cases. This fact suggests the rash may represent a continuum of the same entity, the most severe manifestation of which was a fatal case of Stevens-Johnson Syndrome related to BMS-753493.

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