SYNOPSIS

Final Clinical Study Report for Study CA190001

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 and efficacy of BMS-753493 in subjects with advanced cancer. The investigational drug, BMS-753493, a folate conjugate of an epothilone analog BMS-748285, is 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, 4, 8 and 11 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 initiated 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, 26 subjects were treated, and all completed the study. Phase 2 of the study was not conducted due to early termination of the study.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Subject disposition and demographic characteristics are presented in the following tables.

Subject Disposition: All Treated Subjects

	BMS-753493 (mg)					Total
	5 (N=3)	10 (N=5)	17 (N=7)	26 (N=7)	33 (N=4)	(N=26)
Treated and completed, n (%)	3 (100)	5 (100)	7 (100)	7 (100)	4 (100)	26 (100)
Off treatment, n (%)	3 (100)	5 (100)	7 (100)	7 (100)	4 (100)	26 (100)
Reason for Off treatment, n (%)						
Disease progression	2 (67)	2 (40)	6 (86)	4 (57)	1 (25)	15 (57.7)
Adverse event[a]	1 (33)	0	0	0	0	1 (3.8)
Study drug toxicity	0	1 (20)	0	3 (43)	2 (50)	6 (23.1)
Subject request to discontinue	0	1 (20)	0	0	1 (25)	2 (7.7)
Others[b]	0	1 (20)	1 (14)	0	0	2 (7.7)

[a] Not related to study medication

[b] Including those lost to follow up and subjects no longer meeting study criteria

Pretreatment Subject Characteristics: All Treated Subjects

	BMS-753493 (mg)					Total
	5 (N=3)	10 (N=5)	17 (N=7)	26 (N=7)	33 (N=4)	(N=26)
Age, (yr)						
Mean (SD)	60 (6)	60 (10)	55 (5)	56 (11)	58 (9)	57 (8)
Min, Max	55, 67	51, 73	48, 62	42, 77	48, 69	42, 77
Gender, n (%)						
Male	1 (33)	2 (40)	2 (29)	3 (43)	2 (50)	10 (39)
Female	2 (67)	3 (60)	5 (71)	4 (57)	2 (50)	16 (61)
Race, n (%)						
White	3 (100)	4 (80)	5 (71)	6 (86)	4 (100)	22 (85)
Black/African American	0	0	1 (14)	1 (14)	0	2 (8)
Asian	0	1 (20)	0	0	0	1 (4)
Other	0	0	1 (14)	0	0	1 (4)
Ethnicity, n (%)						
Not Hispanic/Latino	2 (67)	2 (40)	6 (86)	4 (57)	4 (100)	18 (69)
Not reported	1 (33)	3 (60)	1 (14)	3 (43)	0	8 (31)

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

SUMMARY OF SAFETY RESULTS: Adverse events reported during the study are provided in the table below.

Overall Safety Summary: All Treated Subjects

	BMS-753493 (mg)					Total
	5 (N=3)	10 (N=5)	17 (N=7)	26 (N=7)	33 (N=4)	(N=26)
Deaths, n (%)						
Overall	1 (33.3)	0	3 (30.0)	1 (20.0)	3 (100)	8 (30.8)
Cause of death						
Disease progression	1 (33.3)	0	3 (30.0)	1 (20.0)	3 (100)	8 (30.8)
At least one AE, n (%)						
Any grade	3 (100)	5 (100)	7 (100)	7 (100)	4 (100)	26 (100)
Grade 3	1 (33.3)	2 (40.0)	4 (57.1)	3 (42.9)	4 (100)	14 (53.8)
Grade 4	1 (33.3)	0	0	0	0	1 (3.8)
At least one SAE, n (%)						
Any grade	2 (66.7)	2 (40.0)	5 (71.4)	1 (14.3)	3 (75)	13 (50.0)
Grade 3	1 (33.3)	1 (20.0)	3 (42.9)	0	3 (75)	8 (30.8)
Grade 4	1 (33.3)	0	0	0	0	1 (3.8)
AE leading to discontinuation, n (%)						
Any grade	1 (33.3)	2 (40.0)	2 (28.6)	4 (57.1)	3 (75.0)	12 (46.2)
Grade 3	0	0	2 (28.6)	2 (28.6)	3 (75.0)	7 (26.9)
Grade 4	1 (33.3)	0	0	0	0	1 (3.8)

Overall, death due to disease progression was reported in 31% (8 subjects) of treated subjects. The overall proportion of subjects with at least one serious adverse event (SAE) in subjects treated with BMS-753493 was 50% (13 subjects). Two SAEs (vomiting and dehydration) in subjects treated with 26 mg BMS-753493 and 1 SAE (diarrhea) in a subject treated with 33 mg BMS-753493 were considered by the investigator to be possibly related to BMS-753493. Two SAEs (oesophagitis and mucosal inflammation) in subjects treated with 33 mg BMS-753493 were considered to be probably 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 46.2% (12 subjects). No AE leading to discontinuation was reported by more than one subject in any of the treatment cohorts except peripheral sensory neuropathy, reported in 2 subjects (28.6%) treated with 26 mg BMS-753493. Eleven AEs leading to discontinuation in 7 subjects were considered by the investigator to be related to BMS-753493. This included 3 possibly related AEs leading to discontinuation (one each in subjects treated with 10 mg (dyspnoea), 26 mg (fatigue) and 33 mg (diarrhoea) BMS-753493), 7 probably related (5 AEs in 3 subjects treated with 26 mg of BMS-753493 (palmar-plantar erythrodysaesthesia, aspartate aminotransferase increased, peripheral motor neuropathy, two events of peripheral sensory neuropathy), and 2 AEs in a single subject treated with 33 mg BMS-753493 (oesophagitis and mucosal inflammation) and 1 certainly related (rash) in a subject treated with 26 mg BMS-753493.

All study subjects ended treatment. The reasons for ending treatment included disease progression in 15 subjects, study drug toxicity in 6 subjects, an adverse event not related to drug in 1 subject, a request for discontinuation in 2 subjects, and other reasons in 2 subjects.

Of the 12 subjects who were reported to have an AE leading to discontinuation, end of treatment status included disease progression in 4 subjects, study drug toxicity in 6 subjects, an adverse event unrelated to study drug in 1 subject, and lost to follow-up in one subject.

All study subjects experienced at least one AE during the study, 96.2% (25 out of 26 subjects) had AEs related to BMS-753493.

Five of the 26 subjects had dose limiting toxicities (DLTs), which included 1 subject treated with 17 mg BMS-753493 (2 doses were skipped due to Grade 2 Asparatate aminotransferase (AST) elevation), 1 subject (2 doses were skipped due to Grade 2 AST elevation), treated with 26mg BMS-753493 and 3 subjects treated with 33 mg BMS-753493 (Grade 3 diarrhea, Grade 3 oesophagitis, Grade 3 mucosal inflammation, 2 doses were skipped due to Grade 2 Alanine aminotransferase elevation). The maximum tolerated dose (MTD) was determined to be 26 mg. 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 platelets, hyponatremia, hypocalcemia, hypokalemia, low phosphorus, elevated alanine transaminase, elevated aspartate transaminase, elevated alkaline phosphatase, increased total bilirubin and increased albumin values. A marked laboratory abnormality was only reported as an AE when the treating investigator found the abnormality to be clinically significant.

Events of clinical interest included: elevations in aminotransferases in >50% of subjects, however some of these elevations were not considered clinically significant and therefore were not reported as adverse events. Other events of clinical interest include fluid retention characterized by peripheral oedema (2 subjects, 7.7%, all Grade) with or without ascites, neuropathy (6 subjects, 23.1%, all Grade), rash (2 subjects, 7.7%, all Grade), mucosal inflammation (2 subjects, 7.7%, all Grade), and hypersensitivity (3 subjects, 11.5%, all Grade). The neuropathy was typically characterized as an exacerbation of pre-existing neuropathy in subjects previously treated with a taxane or platinum. In two subjects, the rash led to discontinuation after dose reduction from 26 to 17 mg BMS-753493, and occurred after 2-3 cycles. Rash was accompanied by increased lacrimation in both subjects. Program-wide, rash was associated with

lacrimation and stomatitis in some cases. This fact suggests this 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 in study CA190002. In study CA190002, BMS-753493 was administered as a 3-5 minute IV infusion once daily on days 1-4 of a 21-day cycle; in all other respects, CA190002 was identical to CA190001.

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