BRISTOL-MYERS SQUIBB COMPANY

TANESPIMYCIN

Final Clinical Study Report for Study KAG-301/CA200004

Synoptic Report

Phase 3 Randomized, Open-Label Clinical Trial of Tanespimycin (KOS-953) Plus Bortezomib Compared to Bortezomib Alone in Patients With Multiple Myeloma in First Relapse

Indication:	Patients with multiple myeloma in first relapse after failure of previous anticancer therapy and/or bone marrow transplantation
Phase:	Phase 3
Study Initiation Date:	05 Feb 2008
Study Completion Date:	15 Mar 2010
Report Date:	25 May 2010
Previous Version of this Report:	None

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

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SYNOPSIS

Synoptic Clinical Study Report for Study KAG-301

TITLE OF STUDY: Phase 3 Randomized, Open-Label Clinical Trial of Tanespimycin (KOS-953) Plus Bortezomib Compared to Bortezomib Alone in Patients With Multiple Myeloma in First Relapse

PURPOSE: This clinical study report presents results for KAG-301, a Phase 3 study of tanespimycin (KOS-953) in combination with bortezomib (BZ) compared with BZ alone. The primary study endpoint was progression-free survival evaluated under European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry (EBMT/IBMTR) criteria and based on the independent review committee assessments. The study was put on hold in March 2009 because of difficulties with drug manufacturing. Because of continuing issues with drug manufacturing and a decision to stop the development program, the study was terminated in December 2009; at the time, 2 subjects were still receiving study drug. These 2 subjects were transferred to an extension study (KAG-126) and the KAG-301 study was closed in March 2010.

NUMBER OF SUBJECTS: A total of approximately 466 subjects were planned for enrollment, equally divided between 2 treatment arms - tanespimycin + BZ and BZ alone. A total of 41 subjects were randomly assigned to treatment; 20 subjects were assigned to and received treatment with tanespimycin + BZ and 21 subjects were assigned to treatment with BZ alone, of whom 19 received treatment.

DISPOSITION, DEMOGRAPHICS, AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Stratification Demographic and Baseline Characteristics – All-Randomized Population

	Tanespimycin + BZ N = 20	BZ Only N = 21	Total N = 41
Prior BZ Therapy			
None	16 (80.0)	17 (81.0)	33 (80.5)
At Least 1 Dose	4 (20.0)	4 (19.0)	8 (19.5)
Screening Serum β_2-Microglobulin Level			
≤ 2.5 mg/L	2 (10.0)	3 (14.3)	5 (12.2)
> 2.5 mg/L	18 (90.0)	18 (85.7)	36 (87.8)
Prior Stem Cell Transplant			
Yes	10 (50.0)	12 (57.1)	22 (53.7)
No	10 (50.0)	9 (42.9)	19 (46.3)
Age (years)			
Mean (SD)	65.6 (7.31)	62.7 (7.46)	64.1 (7.44)
Median	65.5	63.0	63.0
Range	56, 81	43, 74	43, 81

Stratification Demographic and Baseline Characteristics – All-Randomized Population

	Tanespimycin + BZ N = 20	BZ Only N = 21	Total N = 41
Age Category n (%)			
< 75 years	18 (90.0)	21 (100)	39 (95.1)
≥ 75 years	2 (10.0)	0	2 (4.9)
< 50 years	0	1 (4.8)	1 (2.4)
≥ 50 years	20 (100)	20 (95.2)	40 (97.6)
Gender n (%)			
Male	12 (60.0)	12 (57.1)	24 (58.5)
Female	8 (40.0)	9 (42.9)	17 (41.5)
Race n (%)			
White	14 (70.0)	17 (81.0)	31 (75.6)
Black/African American	5 (25.0)	3 (14.3)	8 (19.5)
Native Hawaiian/Other Pacific Islander	0	1 (4.8)	1 (2.4)
Other	1 (5.0)	0	1 (2.4)
Ethnicity n (%)			
Hispanic/Latino	0	2 (9.5)	2 (4.9)
Not Hispanic/Latino	20 (100)	19 (90.5)	39 (95.1)
Region n (%)			
North America	20 (100)	21 (100)	41 (100)
Weight (kg)			
Mean (SD)	87.75 (15.109)	81.87 (21.665)	84.81 (18.675)
Height (cm)			
Mean (SD)	167.87 (7.231)	167.80 (12.733)	167.83 (10.220)
Body Surface Area (m^2)			
Mean (SD)	1.968 (0.1641)	1.909 (0.2993)	1.938 (0.2401)
KPS n (%)			
100	3 (15.0)	5 (23.8)	8 (19.5)
90	10 (50.0)	5 (23.8)	15 (36.6)
80	5 (25.0)	8 (38.1)	13 (31.7)
70	2 (10.0)	2 (9.5)	4 (9.8)
Missing	0	1 (4.8)	1 (2.4)

BZ = bortezomib; KPS = Karnofsky Performance Status.

SUMMARY OF SAFETY RESULTS:

The safety results reported in this study demonstrate that, in general, tanespimycin in combination with BZ was consistent with the known safety profile of tanespimycin. The incidence of liver toxicity was higher in subjects receiving tanespimycin + BZ (35.0%) than in subjects receiving BZ alone (5.3%), but the overall number of subjects in the study was low precluding any definite conclusions.

Summary of Safety - Treated Subjects

	Tanespimycin + BZ	BZ Alone
	N = 20	N = 19
	Number of Subjects (%)	
Deaths – All	5 (25.0)	1 (5.3)
Within 30 Days of Last Dose[a]	3 (15.0)	0
Treatment-Emergent Adverse Events – All	20 (100)	19 (100)
Treatment-Emergent Adverse Events – Peripheral Neuropathy	14 (70.0)	15 (78.9)
Treatment-Emergent Adverse Events – Liver Toxicity	7 (35.0)	1 (5.3)

a None of these deaths were considered by the investigator to be related to study drug.

SUMMARY OF EFFICACY RESULTS:

In the study, 13 of 20 subjects (65.0%) in the tanespimycin + BZ group had an event, defined as either tumor progression by investigator or death due to any cause (provided the death date was within 49 days of the last complete tumor assessment). Eight of 21 subjects (38.1%) in the BZ alone group had tumor progression or death. The median progression-free survival was 7.5 months (95% confidence interval: 3.3, 15.2 months) in subjects assigned to treatment with tanespimycin + BZ and 8.4 months (95% confidence interval: 6.8, 16.4 months) in subjects assigned to treatment with BZ alone. The Cox proportional hazard ratio (tanespimycin + BZ arm relative to BZ alone arm) was 1.52 (95% confidence interval: 0.57, 4.07).

The objective response rate (based on investigator assessment) in the tanespimycin + BZ group was 50% (10 subjects with complete response or partial response, including very good partial response) and 57% in the BZ alone group (12 subjects).

CONCLUSIONS:

- The study was terminated after 41 subjects were randomly assigned to treatment because of difficulty in tanespimycin drug manufacturing.
- The small number of subjects in either treatment group precludes any comparison of efficacy or safety results.
- In general, results reported in this study were consistent with the known safety profile of tanespimycin + BZ.
- A higher incidence of liver toxicity was observed in subjects receiving tanespimycin + BZ than in subjects receiving BZ alone, but the overall number of subjects in the study was low precluding any definite conclusions.

DATE OF REPORT: 25 May 2010