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DASATINIB

Clinical Study Report Addendum for Study CA180261

SYNOPTIC REPORT

A Randomized Double-blind, Multi-center Phase 2 Trial of Exemestane (Aromasin®) plus Dasatinib Versus Exemestane plus Placebo in Advanced Estrogen Receptor-positive Breast Cancer After Disease Progression on a Non-steroidal Aromatase Inhibitor (NSAI)

Indication:	Breast Cancer
Phase:	2
Study Initiation Date:	20-Feb-2009
Study Completion Date:	30-Dec-2012
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:
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SYNOPSIS

Clinical Study Report Addendum for Study CA180261

TITLE OF STUDY: A Randomized Double-Blind, Multi-Center Phase 2 Trial of Exemestane (Aromasin®) plus Dasatinib Versus Exemestane plus Placebo in Advanced Estrogen Receptor-Positive Breast Cancer After Disease Progression on a Non-Steroidal Aromatase Inhibitor (NSAI)

PURPOSE: The purpose of this randomized double-blind, multi-center Phase 2 study was to determine if the tolerability of exemestane plus dasatinib was well-tolerated and whether there was increased progression-free survival (PFS) compared with exemestane plus placebo in subjects with advanced estrogen receptor positive (ER+) breast cancer after disease progression on a NSAI.

The results of this study are being reported in a synoptic format as the study did not meet its objectives. The results of the primary PFS analysis were previously reported in a synoptic clinical study report format (17-Nov-2011). At the time of the initial study report, 26 subjects remained on treatment; all of whom are now off-treatment.

NUMBER OF SUBJECTS: Approximately 156 subjects were planned to be enrolled in this study. A total of 157 subjects were randomized: 79 to Arm A (exemestane plus dasatinib) and 78 to Arm B (exemestane plus placebo). Two subjects were randomized in error; thus 155 subjects were actually treated: 79 in Arm A (exemestane plus dasatinib) and 76 in Arm B (exemestane plus placebo).

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Subject disposition for all treated subjects is presented in the table below:

Subject Disposition: All Treated Subjects

	Dasatinib+ Exemestane N (%)	Placebo+ Exemestane N (%)	Total N (%)
Treated	79 (100.0)	76 (100.0)	155 (100.0)
Off Treatment	79 (100.0)	76 (100.0)	155 (100.0)
Reason off Treatment			
Disease progression	59 (74.7)	69 (90.8)	128 (82.6)
Study drug toxicity	10 (12.7)	2 (2.6)	12 (7.7)
Other	3 (3.8)	3 (3.9)	6 (3.9)
AE unrelated to study drug	3 (3.8)	1 (1.3)	4 (2.6)
Death	2 (2.5)	0	2 (1.3)
Subject request to discontinue study treatment	1 (1.3)	1 (1.3)	2 (1.3)
Subject withdrew consent	1 (1.3)	0	1 (0.6)

AE = adverse event

Baseline demographic characteristics and disease Characteristics for all randomized subjects is presented in table below:

Baseline Demographic and Disease Characteristics (Randomized Subjects)

	Dasatinib+ Exemestane (N=79)	Placebo+ Exemestane (N=78)	Total (N=157)
Age (years)			
Median	63.0	61.5	62.0
Min, Max	34, 85	36, 80	34, 85
Gender (n [%])			
Female	78 (98.7)	78 (100.0)	156 (99.4)
Male	1 (1.3)	0	1 (0.6)
Race (n [%])			
White	68 (86.1)	58 (74.4)	126 (80.3)
Asian	11 (13.9)	19 (24.4)	30 (19.1)
Other	0	1 (1.3)	1 (0.6)
Performance Status (ECOG) (n [%])			
0	46 (58.2)	46 (59.0)	92 (58.6)
1	32 (40.5)	30 (38.5)	62 (39.5)
Not reported	1 (1.3)	2 (2.6)	3 (1.9)
Time from initial diagnosis to randomization (months)			
Median	67.5	65.4	66.1
Min, Max	6.5, 309.4	5.4, 268.0	5.4, 309.4
Symptomatic Bone Disease (n [%])			
No	48 (60.8)	46 (59.0	94 (59.9)
Yes	31 (39.2)	32 (41.0)	63 (40.1)
Setting of NSAI (n [%])			
Adjuvant	27 (34.2)	27 (34.6)	54 (34.4)
Advanced	52 (65.8)	51 (65.4)	103 (65.6)

ECOG = Eastern Cooperative Oncology Group; NSAI = Non-Steroidal Aromatase Inhibitor

SUMMARY OF SAFETY RESULTS:

The toxicities evident in this trial were those already known to be associated with dasatinib and / or exemestane. The overall tolerability of dasatinib was not generally acceptable in this subject population; particularly when added to well-tolerated hormonal therapy using exemestane.

A summary of the safety results is given in the table below.

Summary of Safety Results (Treated Subjects)

	Dasatinib+ Exemestane (N=79)	Placebo+ Exemestane (N=76)	Total (N=155)
All Death	12 (15.2)	5 (6.6)	17 (11.0)
Death within 30 days of last dose	4 (5.1)	3 (3.9)	7 (4.5)
All SAEs	24 (30.4)	17 (22.4)	41 (26.4)
Drug-related SAEs	10 (12.7)	3 (3.9)	13 (8.3)
AEs leading to discontinuation	21 (26.6)	5 (6.6)	26 (16.7)
Drug-related AEs leading to discontinuation	12 (15.2)	2 (2.6)	14 (9.0)

Summary of Safety Results (Treated Subjects)

	Dasatinib+ Exemestane (N=79)	Placebo+ Exemestane (N=76)	Total (N=155)
All AEs	77 (97.5)	67 (88.2)	144 (92.9)
Drug-related AEs	69 (87.3)	49 (64.5)	118 (76.1)
Drug-related Grade 3/4 AEs	26 (32.9)	8 (10.5)	34 (21.9)

AEs = adverse events; SAEs = serious adverse events

EFFICACY RESULTS:

Progression-free survival was not significantly different in the dasatinib arm compared with the placebo arm (Hazard ratio [HR] = 0.97, 1-sided log-rank P = 0.867). The median PFS was 18.1 weeks in the dasatinib arm vs 15.9 weeks in the placebo arm, representing a 14% increase in median PFS.

The response rate (RR) was 16% (95% CI: 7.2%, 29.1%) for the dasatinib arm and 4% (95% CI: 0.5%, 14%) for the placebo arm. The clinical benefit rate (CBR) was 46% (95% CI: 31.8%, 60.6%) for the dasatinib arm and 34.6% (95% CI: 21.6%, 49.6%) for the placebo arm.

CONCLUSIONS:

- The toxicities evident in this trial were those already known to be associated with dasatinib. The addition of dasatinib to exemestane was not well tolerated compared with exemestane alone.
- In this patient population, the addition of dasatinib to exemestane has not produced a statistically significant increase in PFS.

DATE OF REPORT: 30-May-2013