SYNOPSIS

Final Clinical Study Report for Study CA163140

TITLE OF STUDY: Randomized Phase 2 study of Ixabepilone Plus Trastuzumab vs. Docetaxel Plus Trastuzumab in Female Subjects with Her2+ Locally Advanced and/or Metastatic Breast Cancer

PURPOSE: The purpose of this randomized, Phase 2 open-label study was to assess the response rate of subjects with Her2+ locally advanced and/or metastatic breast cancer (not previously treated with chemotherapy or trastuzumab) to treatment with ixabepilone plus trastuzumab and/or docetaxel plus trastuzumab.
The study was terminated as adequate number of subjects could not be enrolled, and hence, the results of the study are being reported in a synoptic format.

NUMBER OF SUBJECTS: Eighty subjects (40 per arm) were planned for randomization in the study. A total of 50 subjects (25 per arm) were randomized into the study, however only 48 subjects were treated. Twenty-four subjects were treated to ixabepilone + trastuzumab: ixabepilone 40 mg/m^2, administered intravenously (IV) over 3 hours once every 3 weeks and trastuzumab 2 mg/kg administered IV weekly (4 mg/kg loading dose). Twenty-four subjects were treated to docetaxel + trastuzumab: docetaxel 100 mg/m^2, administered IV over 1 hour once every 3 weeks and trastuzumab 2 mg/kg administered IV weekly (4mg/kg loading dose).

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:
Subject disposition, demographic characteristics, and pre-treatment chemotherapy regimens are displayed in the tables below.

Subject Disposition: Randomized Subjects

	Ixabepilone + Trastuzumab	Docetaxel + Trastuzumab	Total
All Randomized, N (%)	25	25	50
Never treated[a]	1(4.0)	1(4.0)	2(4.0)
Treated	24(96)	24(96)	48(96)
No. of Subjects who discontinued study[b]	23(95.8)	23(95.8)	46(95.8)
No. of Subjects still on treatment[c]	1(4.2)	1(4.2)	2(4.2)
Reasons for discontinuation of study therapy			
Death	0	1(4.2)[d]	1(2.1)
Disease progression	14(58.3)	13(54.2)	27(56.3)
Maximum clinical benefit	1(4.2)	0	1(2.1)
Other	3(12.5)	2(8.3)	5 (10.4)

Subject Disposition: Randomized Subjects

	Ixabepilone + Trastuzumab	Docetaxel + Trastuzumab	Total
Study drug toxicity	4(16.7)	1(4.2)	5(10.4)
Subject request to discontinue treatment	1(4.2)	2(8.3)	3(6.3)
Subject no longer meets study criteria	0	2(8.3)	2(4.2)
Subject withdrew consent	0	2(8.3)	2(4.2)

[a] 1 subject in the ixabepilone + trastuzumab group had an adverse event and was never treated; in the docetaxel + trastuzumab group, 1 subject withdrew consent

[b] Percentages based on the number of subjects who received treatment

[c] were switched to trastuzumab monotherapy due to hematological toxicity

[d] Death was after 30 days of last dose of study drug

Baseline and Demographic Characteristics - Randomized Subjects

	Ixabepilone + Trastuzumab	Docetaxel + Trastuzumab	Total
N	25	25	50
Gender			
Female, n (%)	25 (100)	25 (100)	50 (100)
Race			
White, n (%)	25 (100)	25 (100)	50 (100)
Age (years)			
Median	52.0	53.0	52.5
Min-Max	29.0-71.0	37.0-82.0	29.0-82.0
KPS[a]			
100	15 (60.0)	15 (60.0)	30 (60.0)
90	5 (20.0)	9 (36.0)	14 (28.0)
80	4 (16.0)	0	4 (8.0)
70	1 (4.0)	0	1 (2.0)
Not reported	0	1 (4.0)	1 (2.0)
Number of subjects who received prior chemotherapy in neoadjuvant/adjuvant setting	8(32.0)	8(32.0)	16(32.0)

[a] Karnofsky performance status

SUMMARY OF SAFETY RESULTS:

- Overall, 2 subjects (1 from each treatment group, respectively) died during the study. One subject in the ixabepilone + trastuzumab group died due to study drug toxicity of aplasia within 30 days of the last dose of study therapy and one subject in the docetaxel + trastuzumab group died due to respiratory failure, 46 days after the last dose of study drug administration.
- Serious adverse events (SAEs) were reported in 6 (25%) subjects in the ixabepilone + trastuzumab group and in 13 (54.2%) subjects in the docetaxel + trastuzumab group. Drug-related SAEs were reported in 3 (12.5%) subjects in the ixabepilone + trastuzumab group and in 10 (41.7%) subjects in the docetaxel + trastuzumab group.
- All of the study subjects experienced at least one drug-related AE during the study.
- Adverse events leading to discontinuation were reported for 5 (20.8%) subjects in the ixabepilone + trastuzumab group and for 9 (37.5%) subjects in the docetaxel + trastuzumab group. All these reported events were drug-related. Among the 5 subjects in the ixabepilone + trastuzumab group, 4 subjects discontinued treatment due to study drug toxicity and 1 was off the treatment due to disease progression. In the docetaxel + trastuzumab group, 3 subjects discontinued treatment due to disease progression, 1 subject did not meet the study criteria, 2 subjects were off the treatment due to other reasons, 1 subject discontinued treatment due to study drug toxicity, 1 subject withdrew consent and 1subejct requested to be discontinued from the treatment.
- Neutropenia was recorded as a laboratory abnormality in 20 (87.0%) subjects in the ixabepilone + trastuzumab group and in 22 (95.7%) subjects in the docetaxel + trastuzumab group. Fourteen (60.9%) and 22 (95.7%) subjects experienced Grade 3-4 neutropenia in the ixabepilone + trastuzumab and docetaxel + trastuzumab groups, respectively.
- One (4.2%) subject in the ixabepilone + trastuzumab group experienced drug-related Grade 3 febrile neutropenia. No Grade 4 febrile neutropenia was reported in this treatment group. In the docetaxel + trastuzumab treatment group, 7 (29.2%) subjects experienced drug-related febrile neutropenia; 3 (12.5%) were Grade 3 and 4 (16.7%) were Grade 4.
- Drug-related peripheral neuropathy was reported for 16 (66.7%) subjects in the ixabepilone + trastuzumab group and for 11 (45.8%) subjects in the docetaxel + trastuzumab group, respectively.

Overall Safety Summary:-All Treated Subjects

	Number of subjects, N (%)	
	Ixabepilone + Trastuzumab	**Docetaxel + Trastuzumab**
N	24	24
Deaths	1 (4.1)	1 (4.1)
Death within 30 days of last dose of study therapy	1 (4.1)	0
Serious Adverse Events (SAE)		
Any Grade	6 (25)	13 (54.2)
Grade 3-4	4 (16.7)	12 (50)

Overall Safety Summary:-All Treated Subjects

	Number of subjects, N (%)	
	Ixabepilone + Trastuzumab	**Docetaxel + Trastuzumab**
Drug-related SAE		
Any Grade	3 (12.5)	10 41.7)
Grade 3-4	2 (8.4)	8 (34.8)
Adverse events		
Any Grade	24 (100)	24 (100)
Grade 3-4	19 (79.1)	23 (95.8)
Drug-related AE		
Any Grade	24 (100)	24 (100)
Grade 3-4	18 (75)	22 (91.6)
AEs leading to discontinuation of study therapy		
Any Grade	5 (20.8)	9 (37.5)
Grade 3-4	2 (8.4)	4 (16.7)
Drug-related peripheral neuropathy		
Any Grade	16 (66.7)	12 (50)
Grade 3-4	2 (8.4)	0

N - Number of subjects

EFFICACY RESULTS:

The median number of courses of ixabepilone and docetaxel administered per subject was 8.0 (min - max range of 1.0-36.0 courses for the ixabepilone + trastuzumab group and range of 2.0-34.0 courses for the docetaxel + trastuzumab group). The median number of doses of trastuzumab per subject in the ixabepilone + trastuzumab group was 26.0 with a range of 1.0-162.0. The median number of doses of trastuzumab per subject in the docetaxel + trastuzumab group was 30.5 with a range of 1.0-150.0.

An objective response was observed in 15 of 25 (60%) subjects with a 95% confidence interval (CI) of [38.7, 78.9] in the ixabepilone + trastuzumab group and in 13 of 25 (52%) subjects with a 95% CI of [31.3, 72.2] in the docetaxel + trastuzumab group. The difference in the response rates between the ixabepilone + trastuzumab and docetaxel + trastuzumab treatment groups was 9.8% with a 95% CI of (-17.4, 37.0). The objective response rate (ORR) was evaluated as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

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