SYNOPSIS

Final Clinical Study Report for Study CA163139

TITLE OF STUDY: Randomized Phase II Study of Ixabepilone Alone and Ixabepilone Plus Cetuximab as First-Line Treatment for Female Subjects with Triple Negative (ER, PR, Her2 negative) Locally Advanced non-resectable and/or Metastatic Breast Cancer.

PURPOSE: The aim of this study was to estimate the activity of ixabepilone monotherapy 40 mg/m^2 administered once every 3 weeks and the activity of a combination therapy of ixabepilone 40 mg/m^2 administered once every 3 weeks plus cetuximab 250 mg/m^2 administered weekly (400 mg/m^2 loading dose) as first-line treatments in female subjects with triple-negative locally advanced non-resectable and/or metastatic breast cancer (MBC).

The results of this study are being reported in a synoptic format as Bristol-Myers Squibb (BMS) is not currently considering the development of ixabepilone further in this indication. This study was completed as per the study design.

NUMBER OF SUBJECTS:

A total of 79 subjects were randomized of whom 77 subjects were treated (40 subjects to ixabepilone and 37 subjects to ixabepilone + cetuximab) and 2 (randomized to ixabepilone + cetuximab) were not treated.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Pertinent baseline characteristics are shown in the tables below:

Subject Disposition: All Treated Subjects

	Ixabepilone	Ixabepilone + Cetuximab	Total
All Randomized	40 (100)	39 (100)	79 (100)
Never treated[a]	0	2 (5.1)	2 (5.5)
Treated	40 (100)	37 (94.9)	77 (97.5)
No. of Subjects off study therapy[b]	40 (100)	37 (100)	77 (100)
Reasons off study therapy			
Adverse event unrelated to study drug	0	3 (8.1)	3 (3.9)
Death	0	1 (2.7)	1 (1.3)
Disease progression	27 (67.5)	25 (67.6)	52 (67.5)
Maximum Clinical Benefit	3 (7.5)	1 (2.7)	4 (5.2)
Other	2 (5.0)	0	2 (2.6)
Study drug toxicity	7 (17.5)	4 (10.8)	11 (14.3)
Subject request to discontinue study treatment	1 (2.5)	3 (8.1)	4 (5.2)

[a] never treated included a subject no longer meeting study criteria and randomization error in one subject.

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

Pertinent Baseline and Demographic Characteristics: All Randomized Subjects

	Ixabepilone	Ixabepilone + Cetuximab	Total
N	40	39	79
Gender			
Female, n (%)	40 (100)	39 (100)	79 (100)
Race			
White, n (%)	39 (97.5)	39 (100)	78 (98.7)
Black/African American, n (%)	1 (2.5)	0	1 (1.3)
Age (years)			
Median	53	50	53
Min-Max	29-75	31-79	29-79
KPS[a]			
100	23 (57.5)	23 (59.0)	46 (58.2)
90	6 (15.0)	5 (12.8)	11(13.9)
80	11 (27.5)	10 (25.6)	21(26.6)
Not Reported	0	1 (2.6)	1 (1.3)
Setting of prior Chemotherapy[b]			
Adjuvant therapy	28 (70.0)	22 (56.4)	50 (63.3)
Neo-adjuvant therapy	20 (50.0)	20 (51.3)	40 (50.6)
Adjuvant and Neo-adjuvant therapy	8 (20.0)	3 (7.7)	11 (13.9)

[a] Karnofsky performance status

[b] Subjects may have received chemotherapy in more than one setting

SUMMARY OF SAFETY RESULTS:

- Overall, deaths were reported in 17 (22.1%) treated subjects of whom 3 (3.8%) subjects died within 30 days of last dose of study therapy. None of deaths reported were drug-related.
- Serious adverse events (SAEs) were reported for 9 (22.5%) subjects in the ixabepilone group and 12 (32.4%) subjects in the ixabepilone+cetuximab group. Drug-related SAEs were reported in 3 (7.5%) subjects in the ixabepilone group and 6 (16.2%) subjects in the ixabepilone+cetuximab group.
- Adverse events leading to discontinuation were reported for 8 (20%) subjects in the ixabepilone group and 13 (35.1%) subjects in the ixabepilone+cetuximab group. Drug-related AEs leading to discontinuation were reported for 7 (17.5%) subjects in the ixabepilone group and 9 (24.3%) subjects in the ixabepilone+cetuximab group.
- All the study subjects experienced at least one AE during the study. Drug-related AEs were reported in 37 (92.5%) subjects and 37 (100%) subjects in the ixabepilone and ixabepilone+cetuximab treatment groups, respectively.
- Drug-related peripheral neuropathy was reported for 27 (67.5%) subjects in the ixabepilone group and 22 (59.5%) subjects in the ixabepilone+cetuximab group. Grade 3 peripheral neuropathy was reported in 4 (10%) and 4 (10.8%) of subjects in the ixabepilone and ixabepilone+cetuximab group, respectively. None of the events reported were Grade 4
- Drug-related skin and subcutaneous tissue disorders were reported for 25 (62.5%) subjects in the ixabepilone group and 35 (94.6%) subjects in the ixabepilone+cetuximab group. None of the events reported in the ixabepilone group were Grade 3-4. Grade 3 skin and subcutaneous tissue disorders were reported for 5 (13.5%) of subjects in the ixabepilone+cetuximab group and none were Grade 4.

Overall Safety Summary: All Treated Subjects

	Number of subjects (%)	
	Ixabepilone	**Ixabepilone + Cetuximab**
N	40	37
Deaths	8 (20.0)	9 (24.3)
Cause of death		
Disease Progression	8 (20.0)	7 (18.9)
Other Reasons[a]	0	2 (5.4)
At least one SAE		
Any Grade	9 (22.5)	12 (32.4)
Grade 3-4	4 (10)	11 (29.7)
At least one Related SAE		
Any Grade	3 (7.5)	6 (16.2)
Grade 3-4	2 (5.0)	6 (16.2)
At least one AE		
Any Grade	40 (100)	37 (100)
Grade 3-4	21 (52.5)	25 (67.5)
At least one Related AE		
Any Grade	37 (92.5)	37 (100)
Grade 3-4	18 (45.0)	22 (59.4)
AEs leading to discontinuation of study therapy		
Any Grade	8 (20.0)	13 (35.1)
Grade 3-4	3 (7.5)	7 (18.9)

[a] Other reasons included hepatic failure and respiratory distress.

EFFICACY RESULTS:

The primary endpoint of the study was Objective Response (OR). A subject had an OR if her best overall response (BOR) during the study was either a Complete Response (CR) or a Partial response (PR) according to the Response Evaluation Criteria in Solid Tumours (RECIST). An objective response was observed in 12 of 40 (30.0%) subjects, with a 95% confidence interval (CI) of [16.6, 46.5] in the ixabepilone and 14 of 39 (35.9%) subjects with a 95% CI of [21.2, 52.8] in the ixabepilone+cetuximab group.

A total of 38 (95%) of 40 subjects in the ixabepilone and 37 (94.8%) of 39 subjects in the ixabepilone+cetuximab group had progressed or died. The median PFS was similar in both groups (4.1 months). The median time to response was 8.8 weeks in the ixabepilone group and 6.5 weeks in the ixabepilone+cetuximab group.

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