SYNOPSIS

Final Clinical Study Report for Study CA163163

TITLE OF STUDY: A Randomized Phase 2 Study of Ixabepilone Plus Carboplatin and Paclitaxel Plus Carboplatin in Subjects With Advanced Non-Small Cell Lung Cancer.

PURPOSE: The purpose of this Phase 2, randomized, proof-of-concept study was to examine the hypothesis that ixabepilone in combination with carboplatin (ixa/carb) results in superior progression-free survival (PFS) than paclitaxel in combination with carboplatin (pac/carb) for the subgroup of subjects with non-small cell lung cancer (NSCLC) whose tumors were positive for beta-III (βIII) tubulin. Subjects were randomized to the:

Ixa/carb group received ixabepilone administered as a 3 hour intravenous (IV) infusion at a starting dose of 32 mg/m^2 on Day 1 of a 21 day cycle followed by carboplatin administered at a dose calculated to produce an area under the concentration–time curve of 6 mg per milliliter per minute (AUC 6) on Day 1 of a 21 day (ixa/carb group)

Pac/carb group received paclitaxel administered as a 3 hour IV infusion at a starting dose of 200 mg/m^2 on Day 1 of a 21 day cycle followed by carboplatin administered at AUC 6 on Day 1 of a 21 day cycle (pac/carb group)

All subjects randomized to either group of this study were treated for a maximum of 6 cycles or until disease progression or unacceptable toxicity.

At the time of this final clinical study report (CSR), the analysis of PFS was completed (31-May-2010), and evaluation of overall survival (OS) was ongoing. The ixa/carb combination, at the dose and schedule evaluated in this trial, failed to improve PFS relative to the pac/carb group in subjects with NSCLC independent of β III tubulin status. Therefore, this combination would not be further developed in NSCLC and the results of this study are reported in a synoptic format. Results presented in this report would focus on the primary and key secondary objectives.

NUMBER OF SUBJECTS: It was estimated that up to 260 subjects would be randomized 1:1 in this study to yield a total of 104 subjects with βIII tubulin positive tumors. It was planned that study enrollment would end when 104 βIII positive subjects or 260 general population subjects were randomized, whichever comes first. A subject was considered to have an βIII tubulin positive tumor if greater than or equal to 50% of the tumor cells had a βIII tubulin immunohistochemistry staining intensity equal to or greater than that of the positive control (2+). Based on published data, approximately 40 to 50% of subjects with NSCLC were expected to have tumors positive for βIII tubulin.

Of 260 subjects enrolled, 197 were randomized. Among randomized subjects, 191 were administered either ixa/carb (N=95) or pac/carb (N=96) chemotherapy. Among randomized subjects, 104 were classified as βIII+ (53 subjects ixa/carb arm and 51 subjects in the pac/carb arm), and 93 subjects were classified as βIII- (45 subjects in the ixa/carb arm and 48 in the pac/carb arm).

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Subject disposition is presented below.

Subject Disposition - Randomized Subjects

	Number of Subjects (%)		
Overall	Ixa + carb n = 98	Pac + carb n = 99	Total n = 197
βIII tubulin positive	53 (54%)	51 (52%)	104 (53%)
βIII tubulin negative	45 (46%)	48 (48%)	93 (47%)
All Randomized (a)	98 (100.0)	99 (100.0)	197 (100.0)
Never Treated	3 (3.1)	3 (3.0)	6 (3.0)
Treated	95 (96.9)	96 (97.0)	191 (97.0)
Not analyzed for off treatment reason. Subject completed the study therapy (b)	1 (1.1)	0	1 (0.5)
Off Treatment (c)	94 (98.9)	96 (100.0)	190 (99.5)
Reason off treatment (b,c)			
Adverse event (AE) unrelated to study drug	1 (1.1)	4 (4.2)	5 (2.6)
Completed 6 cycles of study drug treatment as per the protocol	47 (49.5)	46 (47.9)	93 (48.7)
Death	3 (3.2)	4 (4.2)	7 (3.7)
Disease progression	27 (28.4)	25 (26.0)	52 (27.2)
Maximum clinical benefit	4 (4.2)	5 (5.2)	9 (4.7)
Other	1 (1.1)	1 (1.0)	2 (1.0)
Study drug toxicity	4 (4.2)	6 (6.3)	10 (5.2)
Subject requested to discontinue study treatment	3 (3.2)	3 (3.1)	6 (3.1)
Subject withdrew consent	4 (4.2)	2 (2.1)	6 (3.1)

a All randomized subjects, by treatment arm as randomized
b Percentages are based on number of subjects who received treatment
c Off all study therapy

Baseline demographics for randomized subjects are presented below.

Baseline Demographics - Randomized Subjects

	βIII Positive			βIII Negative			Overall		
	Ixa + carb	Pac + carb	Total	Ixa + carb	Pac + carb	Total	Ixa + carb	Pac + carb	Total
	n = 53	n = 51	n = 104	n = 45	n = 48	n = 93	n = 98	n = 99	n = 197
Age (Years)									
Median	60.0	60	60	60.0	60.5	60	60.0	60.0	60.0
Min - Max	29.0 - 80.0	43.0 - 80.0	29.0 - 80.0	35.0 - 78.0	34.0 - 85.0	34.0 - 85.0	29.0 - 80.0	34.0 - 85.0	29.0 - 85.0
Gender n (%)									
Male	40 (75.5)	32 (62.7)	72 (69.2)	32 (71.15)	35 (72.9)	67 (72.0)	72 (73.5)	67 (67.7)	139 (70.6)
Female	13 (24.5)	19 (37.3)	32 (30.8)	13 (28.9)	13 (27.1)	26 (28.0)	26 (26.5)	32 (32.3)	58 (29.4)
Race n (%)									
Caucasian	41 (77.4)	38 (74.5)	79 (76.0)	27 (60.0)	38 (79.2)	65 (69.90)	68 (69.4)	76 (76.8)	144 (73.1)
Asian	12 (22.6)	12 (23.5)	24 (23.1)	18 (40.0)	10 (20.8)	28 (30.1)	30 (30.6)	22 (22.2)	52 (26.4)
Other	0	1 (2.0)	1 (1.0)	0	0	0	0	1 (1.0)	1 (0.5)
Karnofsky (PS) n (%)									
100	5 (9.4)	7 (13.7)	12 (11.5)	4 (8.9)	3 (6.3)	7 (7.5)	9 (9.2)	10 (10.1)	19 (9.6)
90	15 (28.3)	22 (43.1)	37 (35.6)	20 (44.4)	21 (43.8)	41 (44.1)	35 (35.7)	43 (43.4)	78 (39.6)
80	24 (45.3)	16 (31.4)	40 (38.5)	17 (37.8)	19 (39.6)	36 (38.7)	41 (41.8)	35 (35.4)	76 (38.6)
70	9 (17.0)	5 (9.8)	14 (13.5)	4 (8.9)	5 (10.4)	9 (9.7)	13 (13.3)	10 (10.1)	23 (11.7)
Not Reported	0	1 (2.0)	1 (1.0)	0	0	0	0	1 (1.0)	1 (0.5)
Cell Type (carcinoma)									
Adenocarcinoma	30 (56.6)	33 (64.7)	63 (60.6)	21 (46.7)	22 (45.8)	43 (46.2)	51 (52.0)	55 (55.6)	106 (53.8)
Broncho-alveolar	1 (1.9)	0	1(1.0)	0	0	0	1 (1.0)	0	1 (0.5)
Large cell carcinoma	2 (3.8)	2 (3.9)	4 (3.8)	1 (2.2)	3 (6.3)	4 (4.3)	3 (3.1)	5 (5.1)	8 (4.1)
Squamous cell	17 (32.1)	13 (25.5)	30 (28.8)	21 (46.7)	21 (43.8)	42 ()	38 (38.8)	34 (34.3)	72 (36.5)

PS = Performance status, Min - minimum, Max - maximum

SUMMARY OF RESULTS:

Efficacy:

The overall Efficacy results are presented in the table below.

Summary of Efficacy Results - Randomized Patients

	Ixa + Carb	Pac + Carb
PFS (Median, Months)	n = 53	n = 51
Beta III Positive	4.27	4.27
80% CI	(3.22, 4.90)	(4.01, 5.42)
Number events/ Number patients at risk (%)	42/53(79.2)	40/51 (78.4)
Hazard ratio (80% CI)	1.04 (0.78, 1.41)	
Long-rank p-value	0.853	
Beta III Negative	n = 45	n = 48
80% CI	5.78	5.32
Number events/ Number patients at risk (%)	(5.32, 6.83)	(4.40, 5.78)
Hazard ratio (80% CI)	27/45 (60.0)	35/48 (72.9)
Long-rank p-value	0.78 (0.55, 1.10)	
	Not calculated (N/C)	
Overall	n = 98	n = 99
80% CI	5.29	5.13
Number events/ Number patients at risk (%)	(4.27, 5.65)	(4.27, 5.59)
Hazard ratio (80% CI)	69/98 (70.4)	75/99 (75.8)
Long-rank p-value	0.92 (0.73, 1.15)	
	0.632	
Best Response, n (%)		
Beta III Positive	n = 53	n = 51
Complete response	1 (1.9)	2 (3.9)
Partial response	8 (15.1)	13 (25.5)
Stable response	32 (60.4)	24 (47.1)
Progressive disease	10 (18.9)	7 (13.7)
Unable to determine	2 (3.8)	5 (9.8)

Summary of Efficacy Results - Randomized Patients

	Ixa + Carb	Pac + Carb
Beta III Negative	n = 45	n = 48
Complete response	0	0
Partial response	12 (26.7)	13 (27.1)
Stable response	23 (51.1)	24 (50.0)
Progressive disease	4 (8.9)	7 (14.6)
Unable to determine	6 (13.3)	4 (8.3)
Overall	n = 98	n = 99
Complete response	1 (1.0)	2 (2.0)
Partial response	20 (20.4)	26 (26.3)
Stable response	55 (56.1)	48 (48.5)
Progressive disease	14 (14.3)	14 (14.1)
Unable to determine	8 (8.2)	9 (9.1)
ORR %		
Beta III Positive	n = 53	n = 51
95 % CI	9/53 (17.0)	15/51 (29.4)
	(8.1 - 29.8)	(17.5 - 43.8)
Beta III Negative	n = 45	n = 48
95 %	12/45 (26.7)	13/48 (27.1)
	(14.6 - 41.9)	(15.3 - 14.8)
Overall	n = 98	n = 99
95 % CI	21/98 (21.4)	28/29 (28.3)
	(13.8 - 30.9)	(19.7 - 38.2)
Time to response		
Beta III Positive	n = 9	n =15
(Median, Weeks)	12.1	6.6
Minimum - Maximum	5.1 - 19.3	5.3 - 18.1

Summary of Efficacy Results - Randomized Patients

	Ixa + Carb	Pac + Carb
Beta III Negative	n = 12	n = 13
(Median, Weeks)	9.5	7.0
Minimum - Maximum	5.0 - 17.4	5.1 - 12.9
Overall	n = 21	n = 28
(Median, Weeks)	12.1	6.6
Minimum - Maximum	5.0 - 19.3	5.1 - 18.1

PFS - progression free survival, CI - confidence interval, ORR - overall response rate,

Safety:

Overall safety summary is presented in the below Table.

Overall Safety Summary

Number (%) of subjects		
	Ixa/carb (n = 95)	**Pac/carb (n = 96)**
Death of any cause	28 (29.5)	34 (35.4)
Any AEs	89 (93.7)	93 (96.9)
Drug-related AEs	85 (89.5)	87 (90.6)
Serious Adverse Events (SAEs)-regardless of relationship	27 (28.4)	28 (29.2)
Drug-Related SAEs	15 (15.8)	9 (9.4)
AEs leading to Discontinuation	11 (11.6)	15 (15.6)

AE - Adverse event, SAE - Serious adverse event.

Death

In the ixa/carb group, 28 deaths (29.5 %) were reported, of which 25 subjects (26.3 %) died due to disease progression and 2 subjects (2.1 %) were due to cardiac arrest and 1 subject (1.1 %) due to cardiac failure. None of these events were related to the study therapy according to the investigator. In the pac/carb group, 34 deaths (35.4 %) were reported of which 30 subjects (31.3 %) died due to disease progression and 1 subject (1.1 %) due to myocardial infarction, 1 subject (1.1%) due to pneumonia and 2 subjects (2.2%) due to unknown reason. None of these events were related to study therapy according to the investigator.

Any adverse events

In the ixa/carb group, 89 subjects (93.7 %) reported at least 1 AE. The most common AEs (occurring in >25% of subjects) were anemia (27 subjects, 28.4 %), decreased appetite (30 subjects, 31.6 %), fatigue (33 subjects, 34.7 %), nausea (subjects 41, 43.2 %), alopecia (45 subjects, 47.4 %), neutropenia (74 subjects, 82.2 %).

In the pac/carb group, 93 subjects (96.9 %), reported at least 1 AE. The most common AEs (occurring in >25% of subjects) were alopecia (55 subjects, 57.3 %), fatigue (30 subjects, 31.3 %), myalgia (29 subjects, 30.2 %), arthralgia (25 subjects, 26.0 %), nausea (31 subjects, 32.3 %), decreased appetite (27 subjects, 28.1 %), neutropenia 73 subjects (79.3%).

Drug related adverse events

In ixa/carb group, 85 subjects (89.5 %) reported at least 1 drug related AE. The most common drug related AEs (occurring in >25 % of subjects) were anemia (27 subjects, 28.4 %), fatigue (29 subjects, 30.5 %), decreased appetite (29 subjects, 30.5 %), neutropenia (32 subjects, 33.7 %), alopecia (45 subjects, 47.4 %).

In pac/carb group, 87 subjects (90.6 %) reported at least 1 drug related AE. The most common drug related AEs (occurring in >25 % of subjects) were decreased appetite (24 subjects, 25.0 %), myalgia (27 subjects, 28.1 %), nausea (29 subjects, 30.2 %), alopecia (55 subjects, 57.3 %).

Drug related peripheral neuropathy:

In ixa/carb group, 35 subjects (36.8 %), reported drug related peripheral neuropathy of which 23 subjects (24.2 %) were noted with Grade 1 peripheral neuropathy and 12 subjects (12.6 %) were noted with Grade 2 peripheral neuropathy. None of the events were more than Grade 2.

In pac/carb group, 54 (56.3 %) subjects, reported drug related peripheral neuropathy of which 25 subjects (26.0 %) were noted with Grade 1, 22 subjects (22.9%) were noted with Grade 2 and 7 subjects (7.3 %) were noted with Grade 3 peripheral neuropathy.. None of the events were more than Grade 3.

Serious adverse events:

In ixa/carb group, 27 subjects (28.4 %) reported at least 1 SAE and 15 subjects (15.8 %) reported at least 1 drug related SAE.

In pac/carb, 28 subjects (29.2 %) reported at least 1 SAE and 9 subjects (9.4 %) reported at least 1 drug related SAE.

Adverse event leading to drug discontinuation:

Adverse event leading to drug discontinuation were reported in 11 subjects (11.6 %) in ixa/carb group and 15 (15.6 %) subjects in pac/carb group. Drug related adverse event leading to discontinuation were reported in 5 (5.3 %) subjects in ixa/carb group and 7 (7.3 %) subjects in pac/carb group.

Laboratory:

In ixa/carb, 31 subjects (34.4 %) and 15 subjects (16.1 %) in pac/carb group were noted with Grade 3-4 leukopenia. In ixa/carb group, 54 subjects (60.0 %) and 51 subjects (55.4 %) in pac/carb group were noted with Grade 3-4 neutropenia. In ixa/carb group, 14 subjects (15.6%) and 1 subject (1.1 %) in pac/carb group was noted with Grade 3 - 4 thrombocytopenia. In ixa/carb group, 15 subjects (16.7 %) were noted with Grade 3 - 4 anemia. There were no subjects noted with Grade 3 - 4 anemia in pac/carb group. Severe anemia and thrombocytopenia were occurring predominantly on ixa/carb group but were manageable and not more frequent than in some historical studies with pac/carb doublet. There were no events of Grade 3 - 4 ALT, and total bilirubin abnormalities. In pac/carb group, 1 subject (1.1 %) was noted with Grade 3 event of AST. None of the subject had Grade 4 event of AST in both the groups. In ixa/carb group, 1 subject (1.2%) was noted with Grade 3-4 event of alkaline phosphatase. In ixa/carb group, 7 subjects (8.3 %) were

noted with Grade 1-2 creatinine level and 6 subjects (6.7 %) in pac/carb group were noted with Grade 1-2 creatinine level. None of the subjects in both the group had Grade 3- 4 creatinine levels.

DATE OF REPORT: 18-Mar-2011