

Interim Safety Results of a Randomized Ph 2 Trial of a Tumor Vascular Disrupting Agent Fosbretabulin Tromethamine (CA4P) with Carboplatin, Paclitaxel and Bevacizumab in Stage IIIB/IV Non-Squamous Non Small Cell Lung Cancer (NSCLC)



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BACKGROUND

Antiangiogenic therapy with bevacizumab added to carboplatin and paclitaxel demonstrates significant clinical benefit in first line NSCLC.¹ Fosbretabulin (CA4P), a reversible tubulin binding vascular disrupting agent (VDA) selectively targets endothelial cells (ECs) of abnormal tumor vasculature causing rapid tumor vessel shutdown.² The central area of tumors is hypoxic and difficult to treat with traditional cytotoxic and radiation therapy. The tumor vessel collapse from fosbretabulin results in necrosis of this central portion of the tumor. Regrowth of tumor vessels (angiogenesis) can occur at the viable outer tumor rim resulting in ongoing tumor cell proliferation. Fosbretabulin enhances the efficacy of several standard cytotoxic agents as well as radiotherapy and antiangiogenic therapy.^{3,4,5,6} The combination of fosbretabulin with bevacizumab was well tolerated in a Phase 1 study of solid organ tumors and some patients showed prolonged stable disease.⁷ Imaging performed showed delayed regrowth of tumor vessels. We hypothesized that the addition of fosbretabulin to standard chemotherapy and bevacizumab in NSCLC would be well tolerated and result in at least additive tumor effects.

PATIENTS AND METHODS

OBJECTIVES

- Primary objectives:**
 Safety and tolerability
 Progression-free survival (PFS)
- Secondary objectives:**
 Overall response rate
 Overall survival

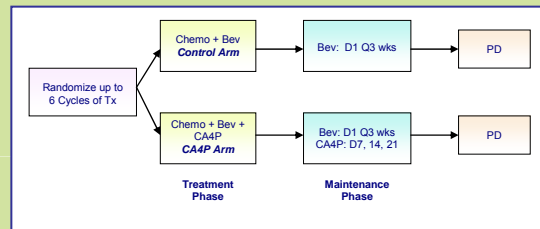
STUDY DESIGN AND EVALUATION

Eligible patients with stage IIIB or IV non-squamous NSCLC were randomized to receive either carboplatin (AUC 6) + paclitaxel (200 mg/m²) + bevacizumab (15 mg/kg) on Day 1 every 3 weeks (Arm 1- Control Arm) or the same regimen every 3 weeks plus CA4P (60 mg/m²) on Days 7, 14 and 21 every 3 weeks (Arm 2- CA4P Arm). Patients who meet all eligibility criteria are randomized to one of two treatment arms in a 1:1 ratio. Randomization is stratified by ECOG performance status (0 vs. 1), and whether or not prior treatment (surgery, radiation) was performed. Patients in both arms receive a maximum of 6 cycles of therapy in the treatment phase and then if they have not had disease progression they enter the maintenance phase. Patients in Arm 1 receive Bevacizumab (15 mg/kg) on day 1 every 3 weeks and patients on Arm 2 receive Bevacizumab (15 mg/kg) on day 1 and fosbretabulin (60 mg/m²) on days 7, 14, and 21 every 3 weeks until disease progression. All patients are followed until death to determine overall survival (OS). (Study Schema). Patients are assessed by RECIST Criteria by the Investigator for tumor response and progression every 8 weeks during the treatment phase and every 3 months during the maintenance phase. A confirmatory CT scan is performed in ~ 4 weeks if a patient achieves a response.

STUDY DESIGN AND EVALUATION (cont.)

Up to 60 patients will be enrolled into this Phase 2 open-label randomized trial. Two interim safety reviews were performed by the Safety Advisory Board (SAB) when the first 10 patients completed cycle 1 and the first 30 patients completed cycle 1. At both time points, the SAB recommended continuing the trial with no changes. The assessment of safety is based on adverse events, laboratory evaluations, ECGs, vital signs and other safety parameters. Patients have frequent safety monitoring with vital signs and ECGs before and following each dose of fosbretabulin during the study. Prevention and management guidelines for hypertension, QTc prolongation and cardiac ischemia have been incorporated into the study and an independent reading facility evaluates ECGs performed during the study.

STUDY SCHEMA



ELIGIBILITY CRITERIA

- Eligibility Criteria (abbreviated)
- Histologically confirmed Stage IIIB of IV non-squamous NSCLC
 - No symptomatic CNS metastasis (CNS mets must be treated)
 - No prior chemotherapy or biologic therapy
 - ECOG performance status 0 or 1
 - Measurable disease per RECIST Criteria (1.0)
 - No history of gross hemoptysis
 - No uncontrolled hypertension (150/100 mm Hg)
 - No history of arterial thrombotic events within the past 6 months
 - Absolute neutrophil count ≥ 1500 cells/uL
 - Adequate hepatic and renal function
 - Normal PTT
 - INR ≤ 1.5
 - No history of gross hemoptysis
 - No concurrent therapeutic anticoagulation

STATISTICAL CONSIDERATIONS

- Sample Size**
 A sample size in each arm of 30 was estimated using a two-sided 95.0% confidence interval approach with large sample approximation. Assuming the 6-month PFS rate in the Control Arm to be around 50%; the PFS for the CA4P Arm will be within the 50% ± 17.9%.
- Analyses Population**
 The safety population of the study consists of all patients randomized who received any amount of study drug. All safety reviews to date were based on the safety population.
- Treatment Emergent Adverse Event Summary**
 Patient adverse events rates were summarized across treatment cycles. The worst severity was used for a given event regardless of relationship to study drug.

RESULTS

Between March 19, 2008 and May 1, 2009, 30 patients were treated with 15 patients on each arm. Median follow-up time was 5.0 months for the Control Arm and 5.1 months for the CA4P Arm. (Table 2). The baseline characteristics were comparable between the 2 treatment arms. (Table 1). Nine (60%) patients on the Control Arm and 6 (40%) patients on the CA4P Arm completed 6 cycles of therapy. (Figure 1). Six patients died: 5 on the Control Arm and 1 on the CA4P Arm. All deaths were from disease progression except one event of fatal hemoptysis on the Control Arm. (Table 3). Concerning hematologic toxicity: grade 3/4 neutropenia on the CA4P Arm was higher than the Control Arm. (Figure 2). Concerning non-hematologic toxicity: grade 3/4 hypertension and cardiac ischemia were higher on the CA4P Arm. (Figure 3). There was no significant difference in chemotherapy dose intensity between the two treatment arms. (Table 2). Of the total planned carboplatin doses, 97.4% of them were actually received on the Control Arm and 94.4% on the CA4P Arm. (Table 2). Of the total planned paclitaxel doses, 96% of them were actually received on the Control Arm and 97.5% on the CA4P Arm. (Table 2). Chemotherapy dose reductions were minimal and comparable between both treatment arms. (Table 2).

DEMOGRAPHICS

Table 1: Patient Baseline Demographics, Safety Population

	Control (n=15)	CA4P (n=15)
Age (years)		
Mean	66	63
Min, Max	51, 81	47, 76
Sex		
Male	8 (53.3%)	10 (66.7%)
Female	7 (46.7%)	5 (33.3%)
Race		
White	10 (66.7%)	13 (86.7%)
Asian	1 (6.7%)	1 (6.7%)
Native Hawaiian or Pacific Islander	2 (13.3%)	0
American Indian or Alaska Native	1 (6.7%)	0
Other	1 (6.7%)	1 (6.7%)
ECOG Status		
0	10 (66.7%)	9 (60%)
1	5 (33.3%)	6 (40%)

EXPOSURE

Table 2: Exposure Summary

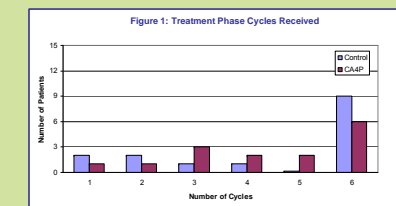
	Control (n=15)	CA4P (n=15)
Planned Carboplatin Total Dose Received	97.4%	94.4%
Planned Paclitaxel Total Dose Received	96%	97.5%
Subjects with Carboplatin Dose Reduction	3 (20%)	2 (13.3%)
Subjects with Paclitaxel Dose Reduction	2 (13.3%)	2 (13.3%)
Median follow up (months)	5.0	5.1

DISPOSITION

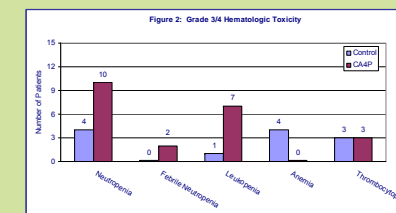
Table 3: Patient Disposition, Safety Population

	Control (n=15)	CA4P (n=15)
Subjects Who Progressed	6 (40%)	3 (20%)
Survival Status		
Subjects Who Died	5 (33.3%)	1 (6.7%)
Death due to Hemoptysis	1 (6.7%)	0
Death due to Disease Progression	4 (26.7%)	1 (6.7%)
Subjects Who are Currently in Treatment Phase	2 (13.3%)	3 (20%)
Subjects Who Completed Six Cycles of Therapy	9 (60%)	6 (40%)
Subjects/Reasons Who Discontinued Early (not PD)	2 (13.3%)	3 (20%)
Adverse Event	1 (6.7%)	1 (6.7%)
Subject Withdrawal or Refusal (not AE)	1 (6.7%)	2 (13.3%)

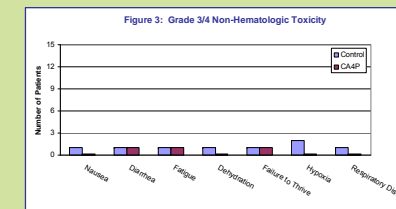
TREATMENT PHASE CYCLES RECEIVED



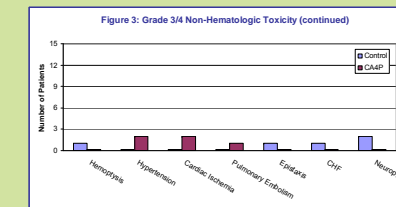
GRADE 3/4 HEMATOLOGIC TOXICITY



GRADE 3/4 NON-HEMATOLOGIC TOXICITY



GRADE 3/4 NON-HEMATOLOGIC TOXICITY (cont.)



CONCLUSIONS

An interim safety review of 30 patients with stage IIIB/IV NSCLC showed that the combination of fosbretabulin with carboplatin + paclitaxel + bevacizumab was well tolerated. The increase in Grade 3-4 neutropenia did not result in a difference in chemotherapy dose intensity between the two treatment arms. Dose reductions and discontinuation of therapy were minimal and comparable between the two treatment arms.

There were no new safety signals or overlapping toxicities with bevacizumab. Clinically significant QTc prolongation was not seen; rates of grade 3/4 hypertension and cardiac ischemia were low.

Most of the deaths were due to disease progression and occurred in the Control Arm. A final analysis of the efficacy and safety of this novel combination will be presented at ASCO 2010.

REFERENCES

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