

# Randomized Phase 2 Trial of a Vascular Disrupting Agent (VDA) Fosbretabulin Tromethamine (CA4P) with Carboplatin, Paclitaxel and Bevacizumab in Stage IIIB/IV Non-Squamous Non Small Cell Lung Cancer (NSCLC): Analyses of Safety and Efficacy of the FALCON Trial

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## BACKGROUND

- CA4P, a reversible tubulin binding vascular disrupting agent (VDA) selectively targets existing tumor vasculature causing vascular occlusion and tumor necrosis.<sup>1</sup>
- Seven early phase studies using imaging to quantify blood flow reductions have confirmed tumor vascular shutdown by CA4P.<sup>2,3</sup>
- Preclinical studies have shown that regrowth of tumor vessels following CA4P treatment can be inhibited by the addition of an antiangiogenic agent such as bevacizumab.<sup>4</sup>
- CA4P combined with bevacizumab was well tolerated with prolonged stable disease in a Phase 1 study of solid tumors.<sup>5</sup>
- This study was designed to study chemotherapy and bevacizumab at full strength combined with a VDA. A concern in past studies was the inability to combine bevacizumab with other agents targeting the vasculature without overlapping toxicities compromising the standard treatment agents.
- A control arm was included so that potential toxicities of agents targeting the vasculature could be compared to toxicities seen with standard therapy.

## METHODS

### OBJECTIVE

To determine the safety, tolerability, and efficacy of CA4P 60 mg/m<sup>2</sup> in combination with carboplatin, paclitaxel and bevacizumab in Stage IIIB or IV NSCLC who had not been treated with chemotherapy or biologic therapy.

### STUDY DESIGN

Males and females age ≥ 18 yrs with histologically confirmed Stage IIIB or IV NSCLC who had not been treated with chemotherapy or biologic therapy.

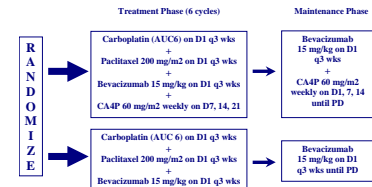
Randomized, multicenter, open-label Phase 2 study

Stratification factors: ECOG (0 or 1) and prior radiation/surgery

Patients received CA4P plus standard therapy (carboplatin + paclitaxel + bevacizumab, C/P/Bev) or C/P/Bev alone every 21 days for up to 6 cycles (Treatment Phase).

Patients without progressive disease (PD) after 6 cycles could continue to receive bevacizumab with or without CA4P (depending on treatment arm) until disease progression (Maintenance Phase).

Figure 1: Study Schema



### MAJOR ELIGIBILITY CRITERIA

- Histologically confirmed Stage IIIB (pleural effusion) or IV non-squamous NSCLC not previously treated with chemotherapy or biologic therapy
- ECOG performance status 0 or 1
- Measurable disease per RECIST (1.0)
- No uncontrolled hypertension (>150/100 mm Hg despite medication)
- No arterial thrombotic events within the past 6 months

## ASSESSMENTS

### Safety

- Physical examination with vital signs
- Laboratory tests
- 12-lead electrocardiograms (ECGs) evaluated by independent reading facility (pre-CA4P dose and 2 and 4 hours post-CA4P dose)
- Adverse events
- Protocol specified prevention and management guidelines for hypertension, cardiac ischemia and QTc prolongation
- Two interim safety reviews by Safety Advisory Board when first 10 patients and first 30 patients completed cycle 1

### Efficacy

- Tumor measurement with CT every 8 weeks during treatment phase and every 12 weeks in maintenance phase
- Tumor response and progression assessment with imaging per RECIST
- All patients followed for overall survival (OS) after disease progression

## EFFICACY / SAFETY EVALUATIONS

### Analyses Populations

All patients randomized and treated are included in the safety analyses.

Intent-To-Treat (ITT) population consisted of all randomized patients and was used for the efficacy analyses.

### Safety and Efficacy Analyses

Adverse events, laboratory evaluations, ECOGs, central read for QTc interval analyses, and vital signs are included. Adverse events are summarized across treatment cycles.

Primary efficacy endpoint is Progression-Free Survival (PFS). Secondary endpoints include OS and Best Overall Response. Point estimates and 95% Confidence Interval (CI) for the above endpoints are presented. No inferential statistics are performed.

## RESULTS

### PATIENT CHARACTERISTICS

- 63 patients randomized: 32 CA4P + C/P/Bev and 31 C/P/Bev
  - 1 CA4P and 2 C/P/Bev were randomized and not treated
- 60 patients treated: 31 CA4P + C/P/Bev and 29 C/P/Bev
- Disease is predominantly Stage IV in both arms

Figure 2: Patient Disposition

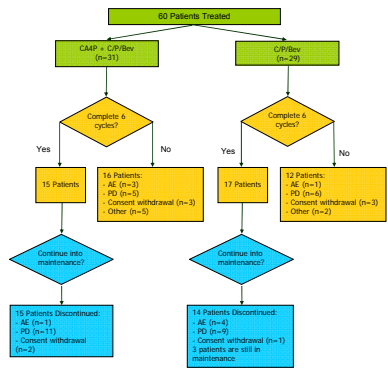


Table 1: Demographics and Baseline Characteristics for All Patients

	CA4P+C/P/Bev (n=31)	C/P/Bev (n=29)
Mean age (years)	61	64
Gender		
Male	19 (61.3%)	12 (41.4%)
Female	12 (38.7%)	17 (58.6%)
Race		
Caucasian	27 (87.1%)	23 (79.3%)
Non-Caucasian	4 (12.9%)	6 (20.7%)
Stage		
IIIB	2 (6.5%)	4 (13.8%)
IV	29 (93.5%)	25 (86.2%)
ECOG Status		
0	16 (51.6%)	16 (55.2%)
1	15 (48.4%)	13 (44.8%)

Table 2: Dose Reduction and Exposure Summary

	CA4P+C/P/Bev (n=31)		C/P/Bev (n=29)	
	Dose Reductions*	Mean Dose Received	Dose Reductions*	Mean Dose Received
Carboplatin	6 (19.4%)	AUC 5.9	8 (27.6%)	AUC 5.9
Paclitaxel	8 (25.8%)	192.9 mg/m <sup>2</sup>	6 (20.7%)	195.5 mg/m <sup>2</sup>
Bevacizumab	4 (12.9%)	14.8 mg/kg	8 (27.6%)	14.4 mg/kg
CA4P	10 (32.3%)	56.9 mg/m <sup>2</sup>	NA	NA

\* Number of patients with dose reductions  
 Note: Chemotherapy and CA4P dose reductions were primarily due to neutropenia  
 Mean total cycles of therapy was 4.6 for CA4P + C/P/Bev vs. 5.0 for C/P/Bev

### SAFETY SUMMARY

- The addition of CA4P to standard therapy was well tolerated
- Safety profiles were similar with CA4P + C/P/Bev and C/P/Bev except:
  - Grade 3 hypertension was more frequent in the CA4P arm and manageable with use of antihypertensive prophylaxis or other anti-HTN medications following protocol management guidelines.
  - Grade 1-4 neutropenia was more frequent on the CA4P arm but there was no difference in dose reductions between the two treatment arms.
- 3 patients experienced transient and reversible cardiac ischemia which resolved within 24-72 hours
- The addition of CA4P to C/P/Bev
  - Slightly increased QTc prolongation (mostly Grade 1 or 2). 3 patients (1 in CA4P arm and 2 in C/P/Bev) had Grade 3 QTc prolongation
  - Did not increase selected bevacizumab-associated safety events such as arterial thrombotic events, proteinuria, or bleeding
- Did not adversely affect renal or hepatic function

Figure 3: Related Hematologic AEs (worst grade per patient)

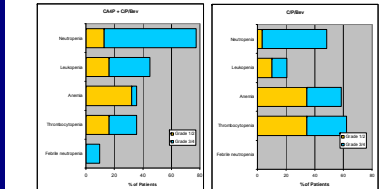
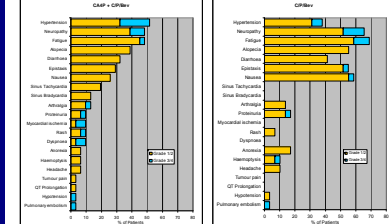
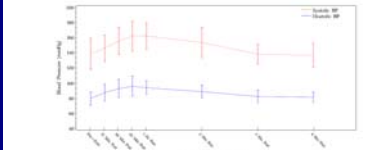


Figure 4: Non-Hematologic Drug Related AEs are summarized across treatment cycles



Toxicity is graded by CTCAE v 3.0  
 Neurotoxicity includes neurotoxicity, neuropathy peripheral, peripheral sensory neuropathy, and neurotoxicity Grade 3 Cardiac Ischemia is symptomatic and testing consistent with ischemia. Grade 2 is asymptomatic Grade 3 Hypertension requires more than one drug or more intensive therapy No Grade 4 cardiac ischemia or hypertension reported.

Figure 5: Blood Pressures (Mean ± SD) for Patients with HTN on CA4P Dosing Days 7, 14, and 21



Summary of all BP values for days on which a patient had an AE of hypertension and received CA4P (Cycles 1-6). There were 32 episodes of HTN in 13 patients in treatment phase.

### CLINICAL ACTIVITY

- Median Follow Up: 11.3 months

Median PFS	ITT	CA4P + C/P/Bev	C/P/Bev
		8.6	9.0
ECOG PS 0	Hazard ratio with 95% CI: 1.05 (0.56, 1.98)	7.0	11.5
		Hazard ratio with 95% CI: 2.38 (1.00, 5.69)	
ECOG PS 1	Hazard ratio with 95% CI: 0.51 (0.23, 1.16)	9.8	3.8
		Hazard ratio with 95% CI: 0.51 (0.23, 1.16)	
PR as Best Overall Tumor Response (ITT)		56%	36%

### EFFICACY SUMMARY

- Higher response rate seen with CA4P + C/P/Bev vs. C/P/Bev. Greater tumor shrinkage was demonstrated in waterfall plots for measurable lesions.
- Standard therapy, C/P/Bev, appears to show greater clinical activity in patients with ECOG PS 0.
- Suggestion of greater clinical activity with CA4P + C/P/Bev in ECOG PS 1 with regard to PFS.

Figure 6: PFS (ITT)

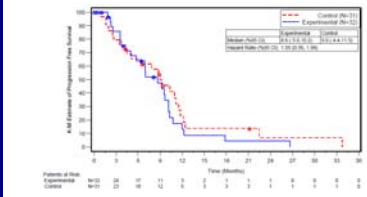


Figure 7: PFS - ECOG PS 0 and 1

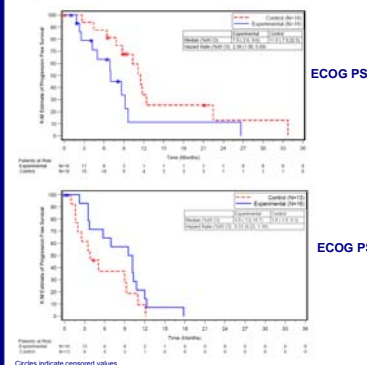
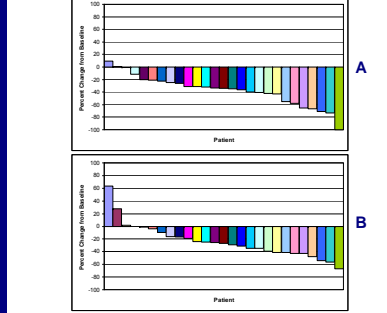


Figure 8: Tumor Size Change from Baseline CA4P+C/P/Bev (A) and C/P/Bev (B)



## CONCLUSIONS

- The addition of CA4P to standard doses of C/P/Bev continues to be well tolerated with trends towards improved response rate.
- Increased neutropenia on the CA4P arm did not result in large differences in dose reductions.
- The addition of CA4P to standard therapy did not impact the ability to complete standard chemotherapy with bevacizumab.
- Hypertension on the CA4P arm was manageable with use of anti-hypertensive medications.
- Suggestion of greater clinical activity with CA4P + C/P/Bev in ECOG PS 1 with regard to PFS. While standard therapy, C/P/Bev, appears to show greater clinical activity in patients with ECOG PS 0.
- CA4P is the first VDA to be successfully administered with bevacizumab in a bevacizumab-eligible NSCLC population and suggests clinical activity in a randomized controlled study.
- A larger trial is needed to verify this suggested differential clinical activity with CA4P + C/P/Bev by ECOG performance status.

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### ACKNOWLEDGMENTS

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