

A phase I/II study of fosbretabulin in combination with everolimus in neuroendocrine tumors that have progressed after at least one prior regimen for metastatic disease.

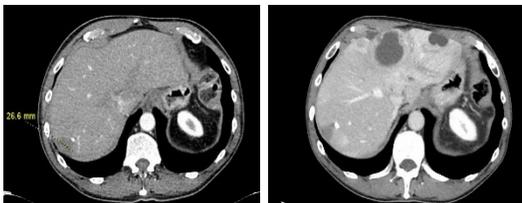


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Fosbretabulin

Fosbretabulin is a novel anti-cancer agent that displays potent and selective toxicity towards tumor vasculature. It is a synthetic, water-soluble, phosphorylated prodrug of the natural product Combretastatin A4 (CA4), which was originally isolated from the bark of the South African bush willow, *Combretum caffrum*. It is the lead compound in a class of agents termed vascular disrupting agents (VDAs). Extensive necrosis with a viable rim of neoplastic cells at the tumor periphery is a characteristic feature of tumors treated with fosbretabulin or other VDAs. A preclinical study in a transgenic mouse model of insulinoma showed a significant decrease in insulin compared to control, with a reduction in the size of tumor along with tumor necrosis and an increase in markers of apoptosis. An additional preclinical study in a rat model of prolactinoma has showed promising activity. A Phase 1 study of fosbretabulin monotherapy in NETs established safety in this population and showed potential efficacy in reducing disease biomarkers and alleviating symptoms.



Study Design

This is an investigator initiated, single center, open label, phase I study involving grade I-III gastroenteropancreatic neuroendocrine tumors, consisting of a dose escalation.

Part A followed by an expansion cohort Part B.

Partial Order Continual Reassessment Method (PO CRM)

Dose Combinations	D1	D2	D3	D4	D5	D6
Everolimus (mg/day)	5	5	7.5	7.5	10	10
Fosbretabulin 60 (mg/m ²)	Every 3 weeks	Every 1 week	Every 3 weeks	Every 1 week	Every 3 weeks	Every 1 week

Sponsors: MCC and Mateon Pharmaceuticals

Study Objectives

Primary Objectives

- To establish the maximum tolerated dose of the combination of everolimus and fosbretabulin in neuroendocrine tumors (Grades 1-3) that have progressed after at least one prior regimen for metastatic disease.

Secondary Objectives

- To establish the safety profile of the combination of everolimus and fosbretabulin in this patient population.
- To observe and record anti-tumor activity. Although the clinical benefit of fosbretabulin plus everolimus has not been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

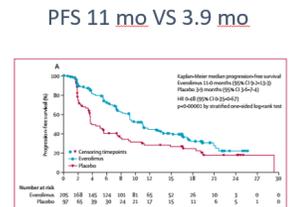
Current Status

Open for accrual: April 2017
Currently we are treating patients in cohort D6
Once MTD is established, we will start Phase II.



Why Everolimus?

- m-TOR inhibitor.
- Tested in over 13 K patients in clinical trials and over 23 K commercially.
- Recently approved for NET based on RADIANT 4 Phase III clinical trial.



Fosbretabulin causes short-lived (4-8 hour) ischemia that leads to extensive tumor necrosis. Everolimus has a longer half-life (30 hours) and slows tumor progression, while also having anti-angiogenic effects. The combination of these two drugs, each with different mechanisms of action, may inhibit tumor growth without additional toxicities.