A phase I 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 Objective and Design

This is an investigator initiated, single center, open label, phase I study involving gastroenteropancreatic neuroendocrine tumor (GEPNET).

Primary Objective: To establish the maximum tolerated dose of the combination of everolimus and fosbretabulin in GEPNETs that have progressed after at least one prior regimen for metastatic disease.

Secondary Objective:

- To establish the safety profile of the combination of everolimus and fosbretabulin in this patient population
- To observe and record anti tumor activity

Sponsors: Markey Cancer Center and Mateon Pharmaceuticals

Dose Combinations	D1	D2	D3	D4	D5	D6
Everolimus (mg/day)	5	5	7.5	7.5	10	10
Fosbretabulin 60 (mg/m2)	Every 3 weeks	Every 1 week	Every 3 weeks	Every 1 week	Every 3 weeks	Every 1 week

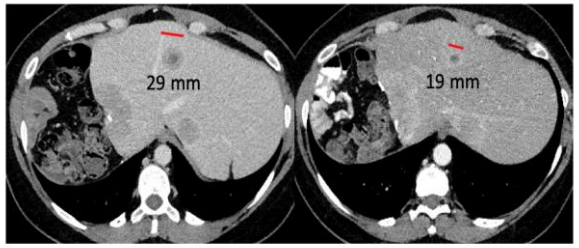
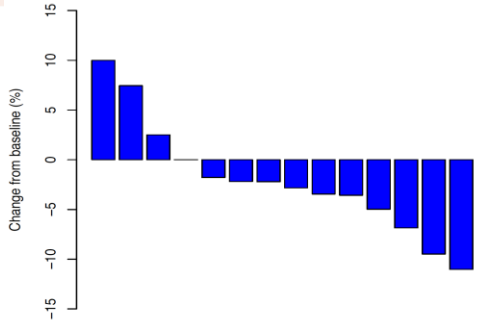


Figure 1: CT scan before and after treatment; 34.5% decrease.



Waterfall plot

Results

- Of the 17 patients enrolled, 16 completed the 12-week trial. One patient was not evaluable due to noncompliance with the treatment regimen.
- No DLTs were observed at day 21.
- **The highest dose of 10 mg daily oral everolimus in combination with weekly 60mg/m2 IV fosbretabulin is the RP2D.**
- No grade 4 or 5 toxicities were noted.
- Grade 3 toxicities were seen in 5 patients that include increased abdominal pain and hyperglycemia (not related to study drug), fatigue (possibly related), decreased lymphocyte count and anemia (related).
- Several patients had delay in treatment due to grade 2 AE's (GI symptoms, rash, thrombocytopenia) and one patient was unable to complete treatment due to pneumonitis.
- Only one patient had radiologic progression at the first q 3 monthly CT scan of chest, abdomen, and pelvis.

Conclusion

Ten mg PO daily everolimus plus 60 mg/m2 fosbretabulin IV weekly is the RP2D.

ClinicalTrials.gov Identifier: NCT0301429