**Complementary therapeutic approach**

BNC105 is a vascular disruption agent that selectively delivers tumor-bound drugs resulting in hypoxia and necrosis. Erlofosfamide (TH-302) is an efficacious agent with FDA regulatory status in 2012. Erlofosfamide is resistive, therapeutic, and under hypoxic conditions selectively releases Br-IPM. Erlofosfamide has low activity under normoxic conditions, but is highly active under hypoxic conditions. Both BNC105 and Erlofosfamide are currently being independently developed by Novartis and Threshold.

Our studies yielded to establish the potential therapeutic combination of BNC105 and Erlofosfamide. It was observed that tumor hypoxia caused by BNC105 will result in increased tumor necrosis attributable to Erlofosfamide. A greater extent of necrosis attributable to Erlofosfamide in BNC105 would increase the area of interest.

- **BNC105** causes an acute disruption of tumor vasculature leading to a rapid increase in tumor hypoxia. Studies were designed to balance the interplay between BNC105 activation by acute hypoxia caused by vessel occlusion and Erlofosfamide.

**Efficacy in triple negative breast cancer model**

BNC105 was shown to have a complementary effect in triple negative breast cancer models. A well tolerated combination was observed.

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**Efficacy in soft tissue sarcoma**

The combination synergistically inhibits growth of MDA-MB-231 breast cancer xenografts with a tumor growth inhibition of 93% compared to vehicle control. Repeat dosing in tumor bearing animals is well tolerated.

**Efficacy in orthotopic renal cancer model**

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**Summary**

BNC105 and Erlofosfamide is a well tolerated combination with dual complementary action designed to leverage the hypoxic activation of Erlofosfamide.

BNC105 and Erlofosfamide can be administered concurrently Day 1 and Day 8 of a 21 day cycle — compatible from a clinical/schedule perspective.

The combination delivered synergistic tumor growth inhibition activity in a MDA-MB-231 triple negative breast tumor model and the RENCA renal orthotopic tumor model.

Significant tumor growth inhibition was observed in the soft tissue sarcoma model when treated with BNC105 and Erlofosfamide compared to treatment with the microtherapeutics alone.

**Driver of efficacy**

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**A well tolerated combination**

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