Background Breast cancer is the most diagnosed cancer and the second leading cause of cancer-related deaths globally among women, frequently due to metastatic disease. CTGF orchestrates diverse multicellular processes including embryonic development, wound healing, and tissue repair. CTGF promotes inflammatory diseases and contributes to cancer cell proliferation, migration, invasion, metastasis, and epithelial-mesenchymal transition. High CTGF is associated with poor prognosis in breast cancer. CTGF-inhibition has shown promise in decreasing metastatic dissemination and sensitizing to cancer cells to chemotherapy in preclinical models. PH-109 is a self-delivering RNAi compound built on proprietary INTASYL™ technology, designed to silence human CTGF with high specificity and without need for specialized formulations or drug delivery systems. PH-109 was originally developed and approved as an investigational new drug (IND) for treatment of dermal hypertrophic scarring (Phase 2; NCT02246465) and subretinal fibrosis (Phase 1/2; NCT02599064). Treatment resulted in a statistically significant reduction of CTGF mRNA and protein at the treatment site, with no significant toxicity or adverse effects. Here we present proof-of-concept (POC) in vivo data showing efficacy of intratumorally administered PH-109 in an orthotopic 4T1 model of metastatic mammary cancer.

Methods PH-109 mediated mRNA silencing of CTGF was validated in 4T1 cells in vitro by RT-qPCR. In vivo, 4T1 cells were implanted into the mammary fat pad of BALB/c mice. When tumors reached threshold volume (150 mm³), animals were randomized into treatment groups; test treatments were administered intratumorally (IT) on Days 1, 4, 7, 10 and 13. Vehicle (PBS), a chemically-identical non-targeting control (NTC) INTASYL or PH-109 at two dose concentrations (0.5 mg; 2 mg) were administered IT; doxorubicin chemotherapy (5 mg/kg) was administered intraperitoneally on Days 1, 7, 13. Tumor volumes and body weights were recorded longitudinally. Primary tumors were resected from each animal at ~500 mm³ in survival surgeries and stained with anti-α-SMA to assess stromal content by immunohistochemistry. Three weeks post-resection animals were euthanized and lungs inflated with India ink and lung macrometastases enumerated.

Results PH-109 provided concentration-associated silencing of CTGF in vitro. In vivo, IT PH-109 elicited antitumor efficacy and improved outcome compared with vehicle- or NTC-treated tumors. In contrast to doxorubicin, PH-109 showed no evidence of toxicity as indicated by weight loss.

Conclusions PH-109 was previously evaluated in over 150 patients without significant toxicity. This, combined with these data in a clinically relevant orthotopic mouse model of metastatic breast cancer, could support accelerated clinical investigation of PH-109 as an anticancer therapeutic.

Ethics Approval Animal studies were performed at Pharma Models LLC, Marlborough, MA 01752, under standard protocol approved by their IACUC.