CLR 2000045, a lipid raft targeted phospholipid-drug conjugate, shows potent activity against multiple breast cancer models including triple negative breast cancer
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INTRODUCTION

Lipid rafts (LR) are cell surface microdomains composed of cholesterol, sphingolipids, glycosphospholipids and signaling receptors. In normal tissue the presence of LR is limited and transient (~2 nanoseconds). In tumors, they have increased presence and are stabilized (up to 10 days).

• LR have been demonstrated to be highly abundant on nearly all tumor types and 100% of individual cancer cells tested. These features combined with providing rapid internalization of phospholipid drug conjugates, makes them an ideal target.

• CLR 2000045 is a phospholipid drug conjugate (PDC) composed of a uniquely designed phospholipid donor conjugated to a novel combretastatin A (CBA) analogue via a cleavable linker. CBAs are potent cytotoxins that inhibit tubulin polymerization within the tumor cell as well as a demonstrated ability to disrupt the local vasculature around/within a tumor.

AIM OF THIS STUDY

Characterization of CLR 2000045’s in vitro uptake and cytotoxicity in multiple breast cancer cell lines, in vivo efficacy and survival benefit in multiple animal models utilizing different types of breast cancer (triple negative and hormone responsive adenocarcinoma).

Materials & Methods

In vitro uptake was assessed using MCF-7 breast cancer cell line and normal human dermal fibroblasts (NHDF) cells and measured via LC/MS/MS. Cells were incubated with 1µM of drug and reported uptake in MCF-7 and NHDF of CLR 2000045 was dosed IV at the following doses 1mg/kg on either day 5 and 12 or day 5, 8, 12 and 15 or day 5, 9, 12, 14, and 16. CLR 2000045 demonstrated a dose response reduction in tumor volume from dose group 1 to dose group 3 (3 times per week for 2 weeks) and at the highest dose tested showed near 100% eradication of the tumor. The 2 highest dose groups showed statistically significant reduction in tumor volume as compared to the vehicle control (p<0.05 and p<0.01 respectively).

• CLR 2000045 provided a statistically significant survival benefit in the TNBC (HCC70) model and the two highest doses were shown to be well tolerated as measured by body weight loss.

CONCLUSIONS

• As with other PDCs tested (data not shown), CLR 2000045 demonstrates significant uptake and release of payload (20-40% of exposed drug) in tumor cell lines while minimal uptake occurs in normal cells.

• CLR 2000045 shows potent in vitro activity against multiple breast cancer cell lines.

• CLR 2000045 demonstrated potent in vivo activity against a triple negative breast cancer model (HCC70) and a metastatic adenocarcinoma breast cancer model (MCF-7).

• CLR 2000045 provided a statistically significant survival benefit in the TNBC (HCC70) model and the two highest doses were shown to be well tolerated as measured by body weight loss.

• These data demonstrate the potent in vitro and in vivo activity of CLR 2000045 against a variety of breast cancer cell lines and animal models and warrants the continued development of this PDC.