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Preclinical development of ELU001 - a folate receptor alpha (FRα)-targeted C'Dot drug conjugate (CDC) for the treatment of brain metastases

Author Block: *Gregory P. Adams*, *Tin Khor*, *Feng Chen*, *Kai Ma*, *Marion Scocca*, *Aranapakam Venkatesan*, *Cathy Reddick*, *Mary Hilgart*, *Thomas Gardinier*, *Fei Wu*, *Melik Turker*, *Peiming Chen*, *Vaibhav Patel*, *Eliel Bayever*. Elucida Oncology, Monmouth Junction, NJ

Abstract:
Antibody-drug conjugates (ADCs) exhibit limited efficacy against brain malignancies due to their inability to cross the blood-brain barrier (BBB) and penetrate into solid tumors. In clinical imaging studies C'Dots readily crossed tumor-disrupted BBB and penetrated across/localized in tumors in the brain avoiding healthy brain. CDCs are ultra-small (6-7 nm) nanoparticles with a silica core coated by short polyethylene glycol chains conjugated to up to 80 small payload and targeting moieties, creating highly potent and avid agents. CDCs' small size mediates rapid renal clearance leading to limited exposure to healthy tissues.

ELU001 is a potent anti-FRα CDC with an average of 21 exatecan topoisomerase-1 inhibitor payload molecules and 13 folic acid targeting molecules on its surface. ELU001 is currently in a dose escalation trial in patients with systemic solid tumor indications that have the potential to overexpress FRα. Early signs of activity with a manageable safety profile have been seen across antigen expression levels.

ELU001 exhibits *in vitro* potency in the sub/low nanomolar range against cancer cell lines that express 3+, 2+ or 1+ levels of FRα. In studies performed in immunodeficient mice bearing intracranial NCI-H2228-luc bioluminescent non-small cell lung cancer tumors, ELU001 was observed to penetrate across disrupted BBB and localize in tumors. Microscopic analysis revealed that ELU001 distributed throughout the tumors but not into the healthy brain. Treatment with a single cycle of ELU001 Q3Dx3 in mice bearing either early (Day 7) or late (Day 14) brain tumors was well tolerated and resulted in significant reduction in tumor burden measured by bioluminescence as well as a prolonged survival benefit. Retreatment of these animals resulted in an additional decrease in tumor burden. These results suggest that ELU001 may have promise for the treatment of metastatic brain tumors that are difficult to treat with currently available agents.

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