Preclinical development of EO1001, a novel irreversible brain penetrating pan-ErbB inhibitor

Wang Shen[1,6], Jeffrey Bacha[1], Sarath Kanekal[1], Neil Sankar[1], Wang ZhenZhong[2], Yasuyuki Yoshida[3], Tomoko Ozawa[3], Tsun-Wen Yao[3], Andrew T. Parsa[4], Jeffrey J. Raizer[4], Shi-Yuan Cheng[4], Alexander H. Stegh[4], Andrew P. Mazar[4], Francis J. Giles[4], Harry D. Pedersen[1], Jann N. Sarkaria[5], Nicholas Butowski[3], Theodore Nicolaides[3], C. David James[4], and Dennis Brown[1,6]

[1]Edison Oncology Holding Corp., Menlo Park, California, [2]Jiangsu Kanion Pharmaceutical Co. Ltd., , Lianyungang, China, [3]University of California San Francisco, San Francisco, California, [4]Feinberg School of Medicine, Northwestern University, Chicago, [5]Mayo Clinic College of Medicine, Rochester, Minnesota, [6]Valent Technologies LLC, Menlo Park, California

Background: The proportion of cancer patients diagnosed with central nervous system (CNS) metastases has increased in recent years due in part to improved systemic disease control by targeted therapies *(Levy 2018, Kotecki 2018).* Patients with tumor progression to the CNS after local treatment have limited therapeutic options. New treatments are needed to address this significant unmet medical need. Signaling by ErbB family members (EGFR, HER2, ErbB4) drives cell proliferation, migration, metabolism and survival. Dysregulation of ErbB mediated signaling is observed in up to 90% of solid tumors resulting in increased cell proliferation and inhibition of apoptosis, conferring a growth advantage and resulting in oncogenic cellular transformation and increased metastatic potential. Cross-talk between ErbB family members has been implicated in the development of acquired resistance to targeted therapy and metastatic events, including CNS metastases *(Brastianos 2015),* suggesting that inhibition of multiple ErbB receptors may result in improved patient outcomes. EO1001 is a novel, patented, oral, brain-penetrating, irreversible pan-ErbB inhibitor targeting EGFR (ErbB1), HER2 (ErbB2) and HER4 (ErbB4) kinases.

Methods: (1) *In vitro* testing. In a panel of over 100 kinases, EO1001 has been shown to have high specificity for the ErbB family of receptors. It has excellent and balanced equipotent activity against all three important ErbB receptors including EGFR, HER2 and HER4 with low nM activity (0.4 to 7.4 nM). EO1001 inhibits signaling downstream of wild type EGFR, mutant EGFR (T790M, L858R and d746-750) and HER2. **(2) PK and toxicity.** In rodent studies *in vivo,* EO1001 exhibited a half-life of 16-20 hours. EO1001 rapidly enters the CNS and penetrates tumor tissue at higher concentrations relative to plasma. Preclinical safety of EO1001 was evaluated by repeat dosing studies in SD rats and beagle dogs. Toxicities typical of the ErbB inhibitor class, including gastro-intestinal effects, weight loss and decreased activity were observed at higher dose groups in both species. Mortality was observed in SD rats at higher dose groups. **(3) *In vivo* efficacy studies.** EO1001 was studied following oral administration in several erbB-positive mouse xenograft models including N87 (Her2+), H1975 (EGFR/T790M), GBM12 (EGFR+), GBM39 (EGVRvIII+). Following oral administration, treatment with EO1001 resulted in a statistically significant improvement in outcomes compared to positive and negative controls in both CNS and systemic tumor models. Treatment with EO1001 was generally well-tolerated with no gastrointestinal side effects observed at efficacious doses in mouse xenograft models.

Conclusion: Based on research conducted to date, EO1001 has the potential to be a best-in-class CNS-penetrating pan-ErbB inhibitor with a safety and pharmacokinetic profile that is amenable for use as a single agent and in combination with other agents. EO1001 is poised to enter phase 1-2a clinical testing in selected cancer indications in 2020.